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The American Journal of Medicine is published monthly by *The American Journal of Medicine, Inc.*, 11 East 36th Street, New York 16, N. Y. Yearly Subscription, \$12.00 U. S. A.; \$13.00 Canada; \$15.00 Foreign, including Latin-American countries, Single Numbers \$2.00; Symposia Numbers \$4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. December, 1957—Volume XXIII, No. 6. Copyright © 1957, by *The American Journal of Medicine, Inc.*

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 11 East 36th St., New York 16, N. Y. Style for bibliography: DOE, J. J. Treatment of hypertension. *Am. J. Med.*, 6: 72, 1948.

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*Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico*, 47:305, Aug., 1955.

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The American Journal of Medicine

Vol. XXIII DECEMBER, 1957 No. 6

CONTENTS

Editorial

- Drug Reactions Characterized by Cholestasis Associated with Intrahepatic Biliary Tract Obstruction A. B. GUTMAN 841

Clinical Studies

- Splenic Venography and Intrasplenic Pressure Measurement in the Clinical Investigation of the Portal Venous System
M. D. TURNER, SHEILA SHERLOCK AND R. E. STEINER 846

This fine study of two recently introduced procedures, percutaneous splenic venography and intra-splenic pressure measurement, demonstrates their general safety and usefulness in appraising the state of the portal venous system. The information so derived may have immediate clinical application, particularly for the patient under consideration for portacaval anastomosis. In demonstrating the presence and capacity of spontaneous portal-systemic shunts, valuable information concerning the pathogenesis of neuropsychiatric disturbances in cirrhotic subjects may be derived; and other practical applications are pointed out. Most important, however, is the better understanding of the anatomic and physiologic principles of increased portal venous system pressure, and the better insight into clinical manifestations which are being acquired as a result of such studies.

- Effect of L-Arginine on Elevated Blood Ammonia Levels in Man
JOHN L. FAHEY, DANIEL NATHANS AND DONALD RAIRIGH 860

The authors found no clinical improvement or lowering of blood ammonia in eight subjects with hepatic encephalopathy (for the most part apparently moribund, with extensive neoplastic replacement of the liver) or in subjects free of liver disease but with elevated blood ammonia induced by intravenous injection of ammonium salts. From these and related studies it is concluded that arginine is effective in preventing or reducing elevation in blood ammonia only by preventing the formation of ammonia in the liver, from certain amino acids, such as glycine. Elevation of blood ammonia derived from exogenous sources, the usual origin in hepatic encephalopathy encountered clinically, is not prevented or alleviated by administration of arginine. This position sounds reasonable but an altogether satisfactory explanation for the conflicting reports on this subject must await further investigation.

- Allergy to Chlorpromazine Manifested by Jaundice LEO E. HOLLISTER 870

Dr. Hollister brings together the evidence that chlorpromazine jaundice is a manifestation of drug allergy and, by adding compelling evidence of his own in the form of recurrence after challenge, makes a strong case. The discussion of this whole vexing problem is enlightened and well worth careful consideration.

Contents continued on page 5

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2. Giordano, A. S., Pope, J. L., and Hagan, B.: Am. J. M. Technol. 27:29, 1956.



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VOLUME TWENTY-THREE

NUMBER SIX

- Familial Cholelithiasis, with Special Reference to Its Relation to Familial Pancreatitis
JOSEPH A. RINALDO AND JAMES I. BALTZ 880

This account of cholelithiasis occurring in high incidence in a family without overt hemolytic disease (although this was not rigorously excluded) would seem to be of sufficient interest to warrant further exploration. It is hinted that some obscure inborn error of lipid metabolism may be at work in these circumstances.

- The Effect of 5-Hydroxytryptamine on Intestinal Motor Function in Man
THOMAS R. HENDRIX, MICHAEL ATKINSON, JAMES A. CLIFTON
AND FRANZ J. INGELFINGER 886

The alimentary tract origin of 5-hydroxytryptamine, originally designated enteramine, suggests the possibility of a local action on the intestine, in addition to its systemic humoral effects. The present study showed that this compound in low dosage did in fact increase tone in the intact small intestine of most of the human subjects studied. This finding, and other indications, suggest that 5-hydroxytryptamine normally may affect the motor activity of the intestine and thus play a physiological role in this respect.

- Confirmation of Achylia by Radioactive B₁₂ Uptake and Blood Pepsin Measurement
I. J. POLINER AND H. M. SPIRO 894

The authors compared the results of the Schilling test, a measure of intrinsic factor activity, and blood pepsin determinations in a number of subjects with intact and impaired gastric secretion. The data afford some further insight into the order and degree of loss of specific gastric secretory functions.

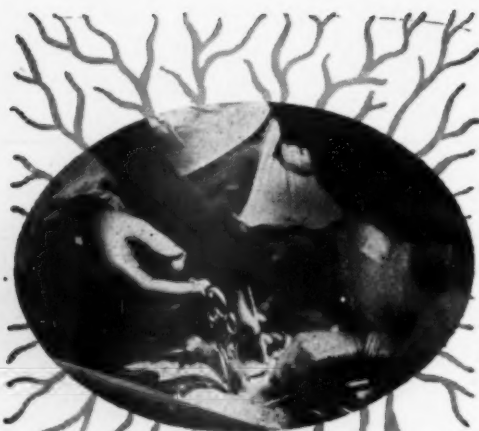
- The Effects of Corn Oil on Serum Lipids in Normal Active Subjects
WILLIAM SHAPIRO, E. HARVEY ESTES, JR. AND HELEN L. HILDERMAN 898

There is now convincing evidence that addition to the diet of substantial amounts of unsaturated oils will effect an unequivocal fall in serum cholesterol. The present study demonstrates this in six normal, ambulatory subjects given 70 per cent of a restricted total fat intake (100 gm./day) in the form of a corn oil emulsion; the mean control serum cholesterol level of 222 mg. per cent fell to 158 mg. per cent after two weeks. When the total fat intake was increased to 170 gm./day the serum cholesterol rose toward the initial levels, despite continued ingestion of 70 gm. of corn oil daily. The possible metabolic significance of this and other changes in serum lipids is interestingly discussed, the authors wisely forbearing prognostication in regard to atherosclerosis. In view of the impressive results, and the growing interest in this form of dietary regulation, the study merits careful perusal.

- Studies in Cushing's Syndrome. I. Observations on the Response of Plasma 17-Hydroxycorticosteroid Levels to Corticotropin
NICHOLAS P. CHRISTY, DONALD LONGSON AND JOSEPH W. JAILER 910

The intention of this study was to clarify the old controversial question as to whether or not Cushing's syndrome associated with bilateral adrenal cortical hyperplasia originates in the hypo-

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CONTENTS continued—December 1957

VOLUME TWENTY-THREE

NUMBER SIX

thalamus, anterior pituitary or adrenal cortex—but again the evidence is conflicting. On the one hand, confirmation was obtained of the exaggerated response of the adrenal cortex to ACTH, and of the resistance to suppression by administration of corticosteroids, which would support the concept of adrenal cortical origin. On the other hand, clinical remission was obtained in some cases by pituitary radiation, which would support the concept of a central origin. These and other findings are discussed instructively.

Review

The Agammaglobulinemias. Relations and Implications

CASIMIR A. DOMZ AND DELBERT R. DICKSON 917

The authors bring together the expanding literature on the congenital and acquired a- and hypogammaglobulinemias, and cite some of their own experiences in this field. This is a subject of unusual interest, with ramifications that involve many questions of basic importance in immunology, as well as practical questions in diagnosis and management of the disorder—all these are discussed in some detail. Not the least pertinent feature is that recurrent infection in agammaglobulinemia can be largely prevented in many instances by simple replacement therapy with normal gamma globulin.

Seminar on Atherosclerosis

Nutritional Factors and Serum Lipid Levels EDWARD H. AHRENS, JR. 928

Dr. Ahrens closes the symposium on atherosclerosis with an informative panoramic view of the present status of knowledge of the relationship of nutritional factors to serum lipid levels. In so doing he does not limit himself to any one foodstuff, out of context as is the common practice, but considers the question rather in terms of an indissociable four component system comprised of fat, protein, carbohydrate and total calories. Each of these nutritional factors is then considered, alone and in relation to the others; special attention is given to the fats, unsaturated fatty acids and cholesterol as dietary constituents and their relationship to atherosclerosis. The whole makes a convincing case for the position that insofar as the rate and magnitude of atherogenesis is affected by the composition of the diet, this effect is the resultant of many interacting factors, not of a preponderance of one food component alone.

Clinico-pathologic Conference

Primary Hyperparathyroidism, Pancreatitis and Peptic Ulcer 953

Clinico-pathologic Conference (Washington University School of Medicine)

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Case Reports

- Paraldehyde Intoxication with Metabolic Acidosis. Report of Two Cases, Experimental Data and a Critical Review of the Literature
JAMES N. HAYWARD AND BURIS R. BOSHELL 965

- Renal Tubular Acidosis with Organic Aciduria during Paraldehyde Ingestion. Six Year Study of an Unusual Case
J. R. ELKINTON, E. J. HUTH, J. K. CLARK, E. S. BARKER AND D. SELIGSON 977

- Metabolic Acidosis Occurring during Administration of Paraldehyde
CHRISTINE WATERHOUSE AND EDWARD A. STERN 987

These three reports deal with a subject of some practical importance, the acidosis produced by overdosage of what is generally considered to be an innocuous drug, paraldehyde, or, more precisely, by the acetaldehyde and acetic acid which accumulate in stored bottles of the unstable parent compound. The first paper, by two alert young residents, provides the background for the clinical considerations, including direct evidence of the deteriorated state of paraldehyde in hospital supply rooms, and cites two cases of metabolic acidosis due to paraldehyde intoxication. The next two reports amplify the subject by recording additional cases and observations. The total experience leaves no doubt about the validity of the points made, and the need for alertness in this connection.

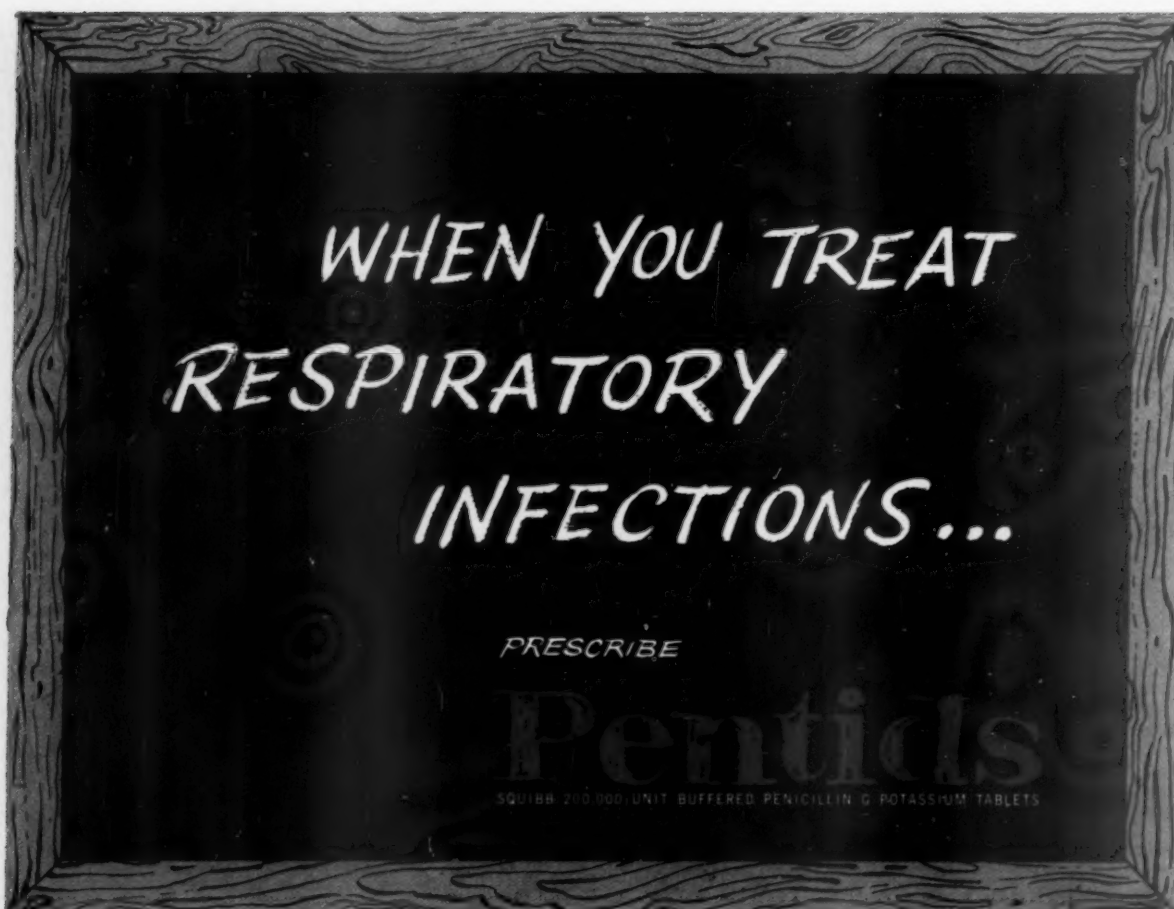
- Ammonia Intoxication during Treatment of Alkalosis in a Patient with Normal Liver Function JOHN C. STAUFFER AND BELDING H. SCRIBNER 990

As the author points out, despite the high incidence of toxic manifestations following administration of ammoniums chloride, particularly when given intravenously, there are few reports specifically describing the appearance of the neurologic picture of hepatic coma in subjects presumed to be free of liver disease. An illustrative case is described.

- Portal Hypertension and Bleeding Esophageal Varices Secondary to Sarcoidosis of the Liver WILLIAM FRAIMOW AND RALPH M. MYERSON 995
A well studied and instructive case.

- Herpes Zoster with Ileus Simulating Intestinal Obstruction
STEVEN J. FIGIEL AND LEO S. FIGIEL 999
An interesting case.

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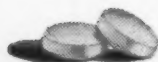
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ERRATUM

In the article "Epidemiology of Coronary Heart Disease" by Dr. George V. Mann, September issue, page 478, the second sentence beginning "Using the reasonably objective criterion of *aortic* calcification . . ." should read ". . . *coronary* calcification."

Advertising Index on page 108

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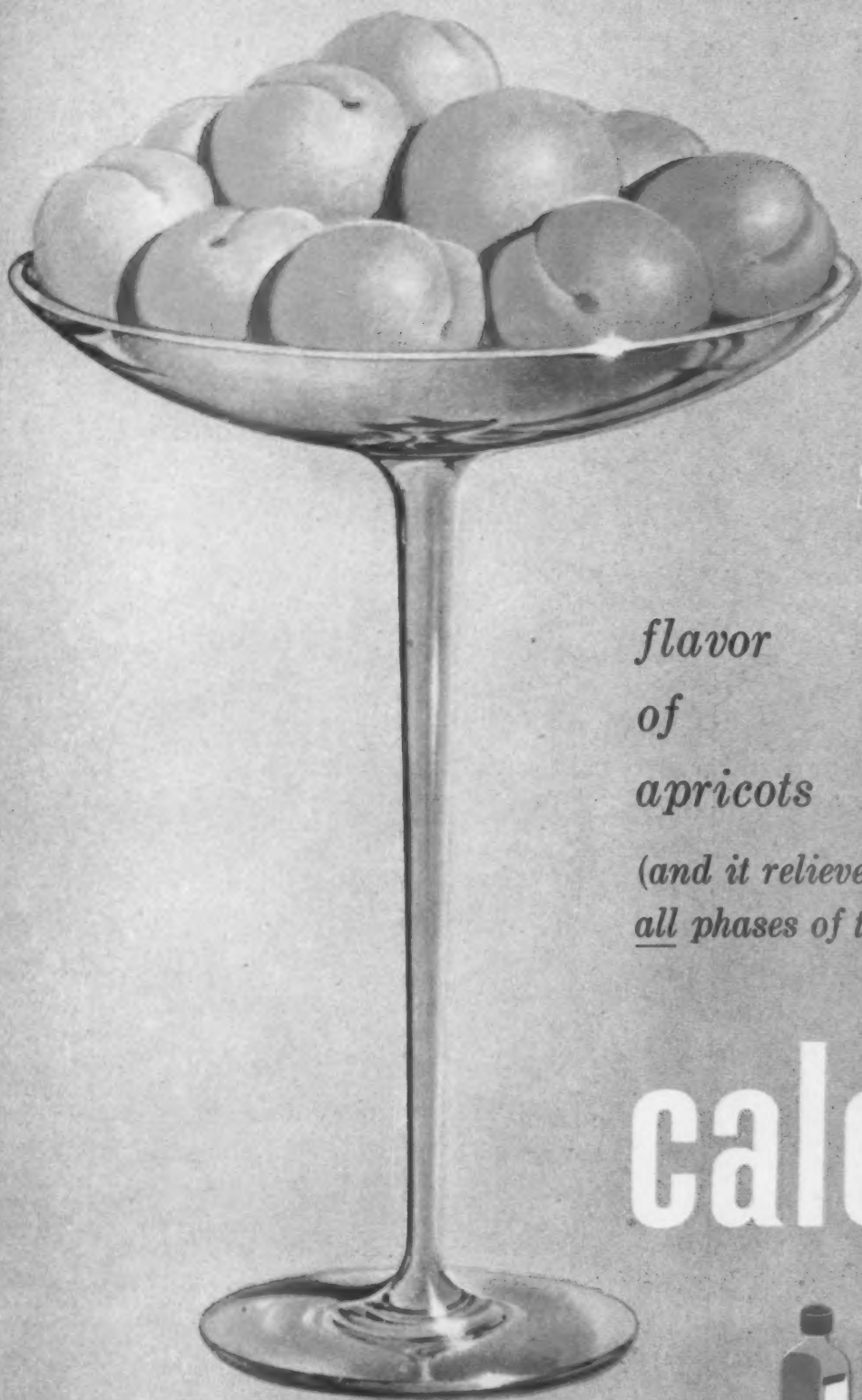
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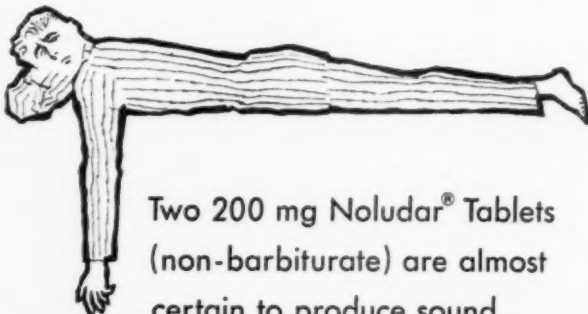
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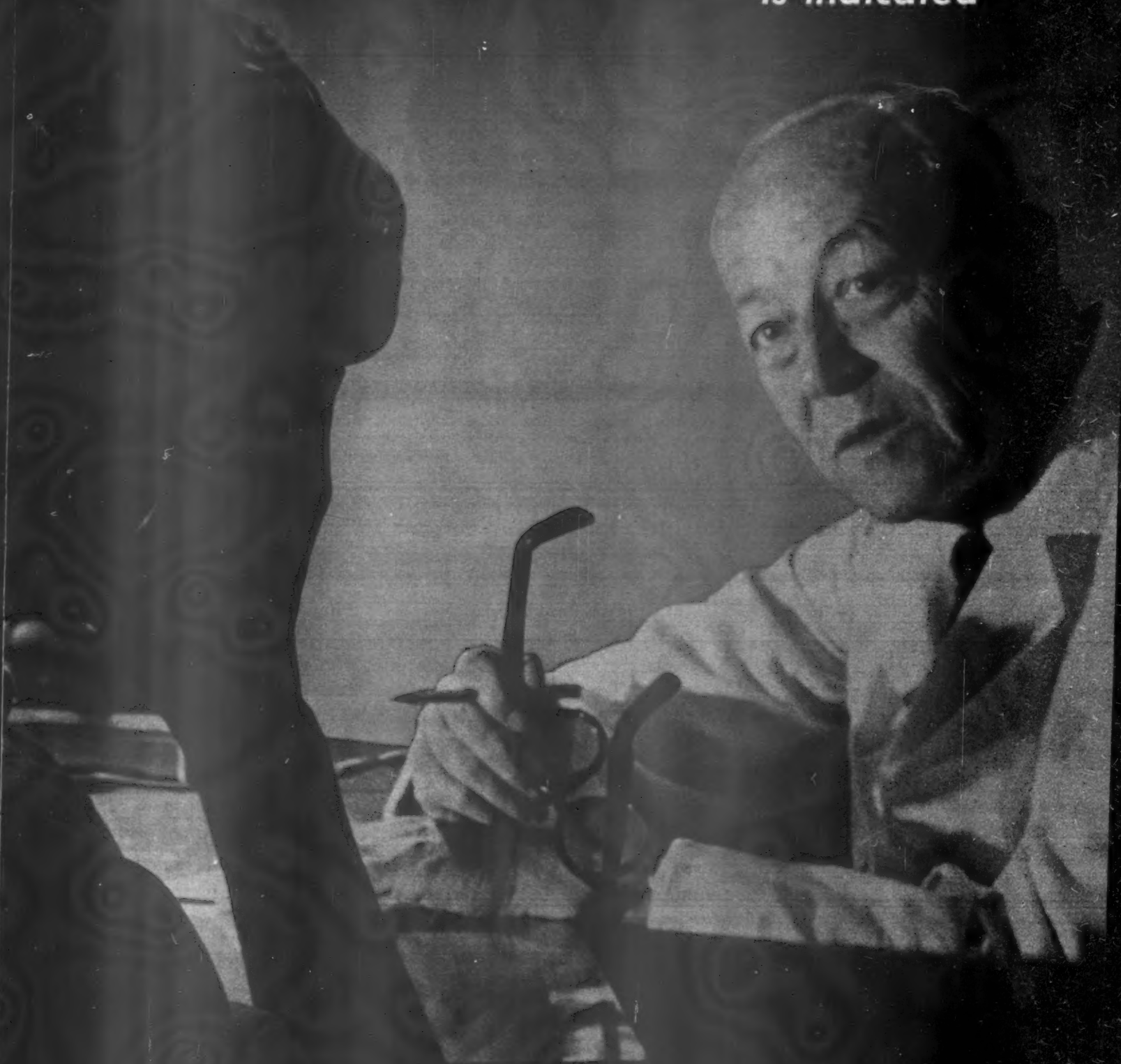
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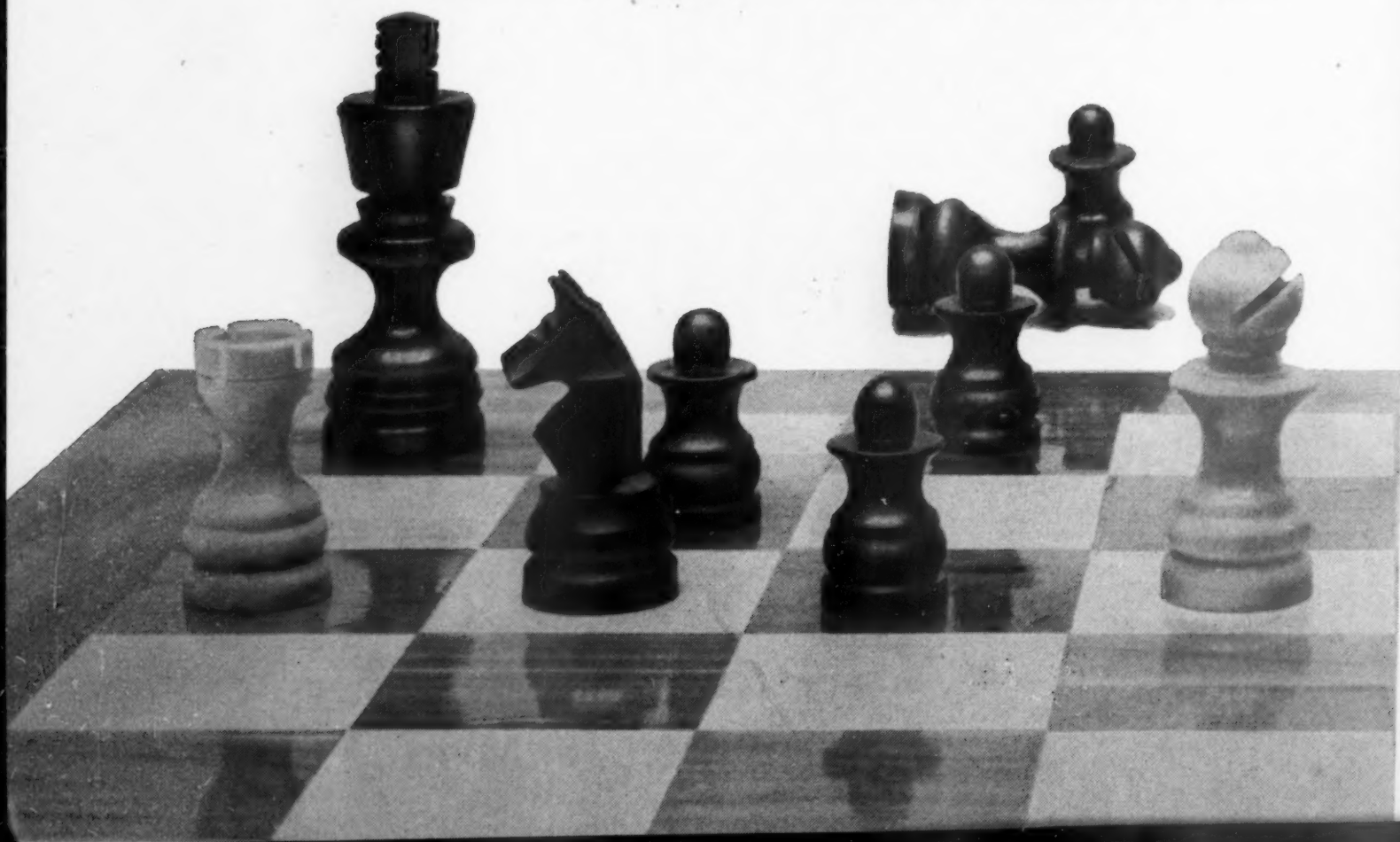
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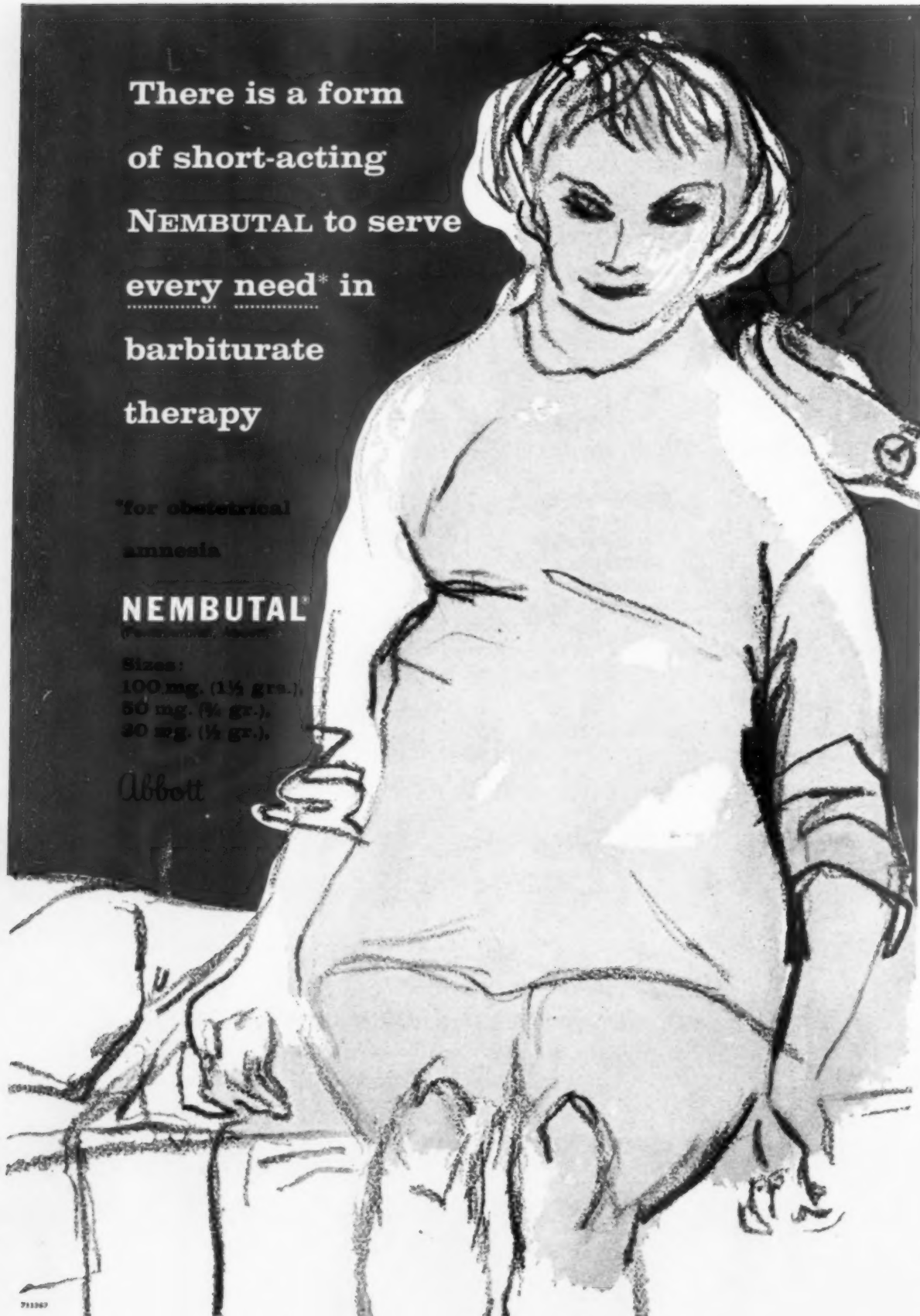
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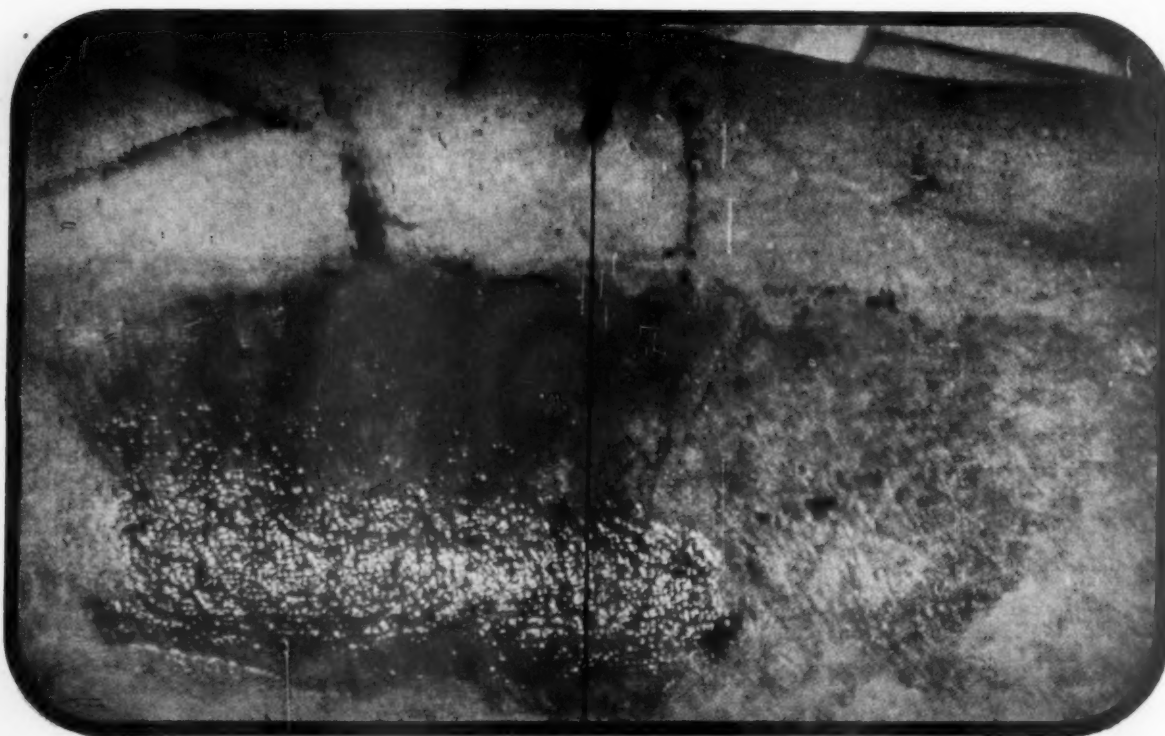
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1. Smith, R. T.: M. Clin. North America, March 1957. 2. Smith, R. T.: New York Med. 5:16, 1952.
3. Lehrer, H. W. et al.: Northwest Med. 75:1249, 1955.



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Jeffords, J. V., and Hagerty, R. F.: *Ann. Surg.* 145:169, 1957.

FURACIN®, . . . brand of nitrofurazone
the broad-range bactericide that is *gentle to tissues*

spread FURACIN Soluble Dressing: FURACIN 0.2% in water-soluble ointment-like base of polyethylene glycols.

sprinkle FURACIN Soluble Powder: FURACIN 0.2% in powder base of water-soluble polyethylene glycols. Shaker-top vial.

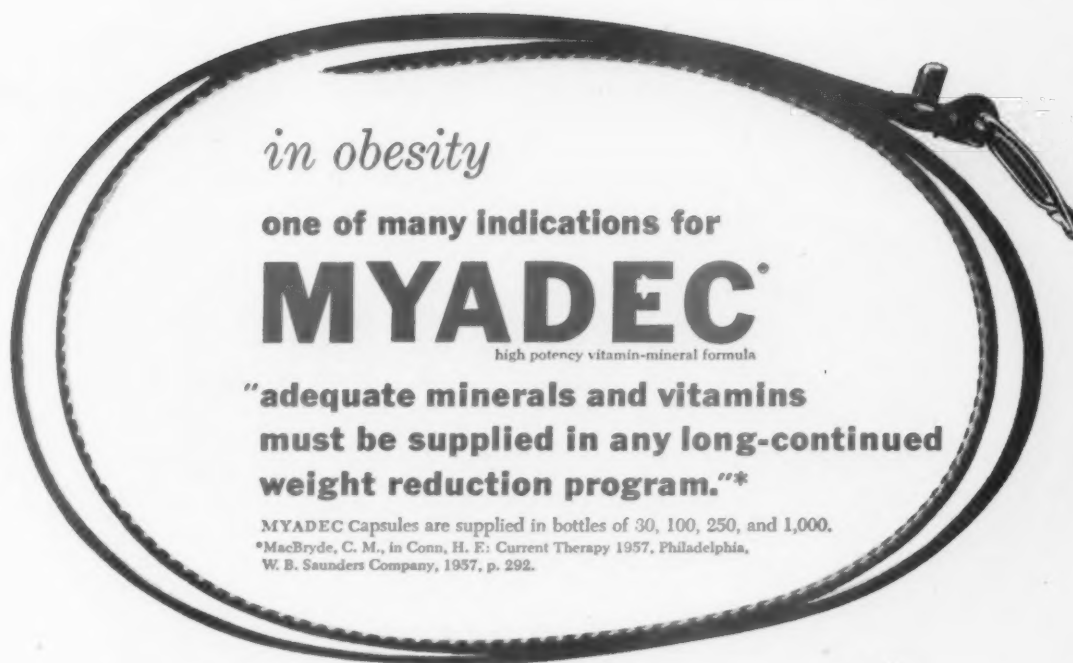
spray FURACIN Solution: FURACIN 0.2% in liquid vehicle of polyethylene glycols 65%, wetting agent 0.3% and water.



EATON LABORATORIES, NORWICH, N.Y.

Nitrofurans—a NEW class of antimicrobials—neither antibiotics nor sulfonamides



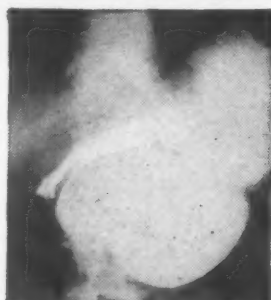


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when anxiety and tension "erupts" in the G. I. tract...

IN GASTRIC ULCER



PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of gastric ulcer — without fear of barbiturate loginess, hangover or habituation . . . with PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime.

Supplied: Bottles of 100, 1,000.



*Trademark

® Registered Trademark for Tridihexethyl Iodide Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK



A.M.

Just two doses—

and



P.M.

LIPO GANTRISIN ROCHE®

... and you can be sure that your patients will have prompt, lasting plasma and urine levels.

Lipo Gantrisin is the ideal pediatric form of Gantrisin, in which 2 doses a day are sufficient to combat most urinary and systemic infections of non-viral — non-rickettsial origin.

ROCHE LABORATORIES • DIVISION OF HOFFMANN-LA ROCHE INC • NUTLEY 10 • N. J.



Lipo Gantrisin® Acetyl—brand of acetyl sulfisoxazole in a homogenized mixture

**NEW LEDERLE
HEMATINIC MARKS
A QUARTER-CENTURY
OF PROGRESS IN
ANTI-ANEMIA
THERAPY**

INTRINSICALLY BETTER

FALVIN

with AUTRINIC

FALVIN FEATURES A NEW KEY COMPONENT—AUTRINIC

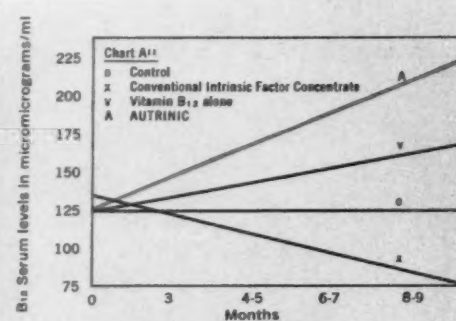
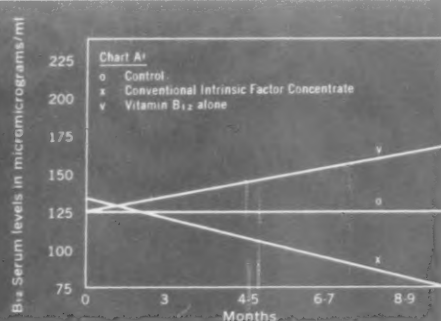
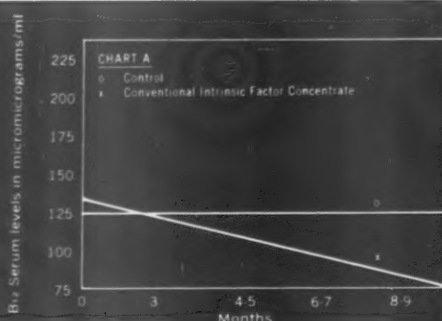
INTRINSIC FACTOR CONCENTRATE

Newer techniques of research have led to the isolation, bio-assay and clinical confirmation of a new, highly active Intrinsic Factor Concentrate.^{1,2}

Despite the efficiency of modern hematinics, their range of usefulness is adversely affected by the inability of the Intrinsic Factor Concentrate used to overcome the inherent limitation on capacity to absorb B₁₂ across the GI mucosal barrier. Age differences as well as individual ranges of variation add to the complex problem of absorption.

Oral administration of Co⁶⁰-labeled B₁₂ has shown that Intrinsic Factor Concentrates now in common use actually decrease B₁₂ absorption. (Charts A and A¹)³

In contrast, AUTRINIC promotes intestinal absorption of B₁₂, resulting in serum B₁₂ levels significantly higher than those obtained either with conventional Intrinsic Factors or with B₁₂ alone. (Chart A¹¹)³



NOW...

A BETTER PATTERN OF RESPONSE IN ANTI-ANEMIA THERAPY

BETTER GASTROINTESTINAL RESPONSE

higher serum B₁₂ levels for normal maturation of tissue as well as blood cells

BETTER NEUROLOGIC RESPONSE

higher serum B₁₂ levels for avoidance of neuropathy

BETTER HEMATOLOGIC RESPONSE

higher serum B₁₂ levels for interaction with Folic Acid, essential to normal erythropoiesis

FALVIN*

HEMATINIC LEDERLE

with **AUTRINIC***
INTRINSIC FACTOR CONCENTRATE WITH B₁₂

INTRINSICALLY BETTER IN ANEMIA

THERAPEUTIC for anemias due to deficiency of recognized hemopoietic elements.

SUPPORTIVE where the anemia is associated with other pathology.

PROPHYLACTIC in marginal deficiency states which may predispose to clinically overt anemias.

Each Capsule contains:

Autrinic® Intrinsic Factor Concentrate with	
vitamin B ₁₂	1 U.S.P. Oral Unit
Ferrous Sulfate Exsiccated	300 mg.
Ascorbic Acid (C)	75 mg.
Folic Acid	1 mg.

Dosage: Two Capsules Daily

REFERENCES:

1. Williams, W. L.; Chow, B. F.; Ellenbogen, L. and Okuda, K.: Intrinsic Factor Preparations which Augment and Inhibit Absorption of Vitamin B₁₂ in Healthy Individuals. In: Vitamin B₁₂ und Intrinsic Factor, edited by Heinrich, H. C.—Ferdinand Enke Verlag, Stuttgart, 1957, P. 250.
2. Williams, W. L.; Ellenbogen, L.; Rabiner, S. F. and Lichtman, H. C.: An Improved Urinary Excretion Test as an Assay for Intrinsic Factor. Proc. Soc. Exper. Biol. & Med. 89: 357 (Nov.) 1955.
3. Adapted from Tauber, S. A.; Goodhart, R. S.; Hsu, J. M.; Blumberg, N.; Kassab, J. and Chow, B. F.; Vitamin B₁₂ Deficiency in the Aged. Geriatrics 12: 368 (June) 1957.



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*Reg. U. S. Pat. Off.

Meat...

and the Protein Need in Renal Disease

Prevailing opinion holds that during the nephrotic state—provided the kidneys are capable of excreting nitrogen in a normal manner—the patient should be given a diet high in protein (1.5 to 2 grams per kilogram of body weight daily). The purpose of such a diet is to replace depleted plasma protein and to increase the colloidal osmotic pressure of the blood.

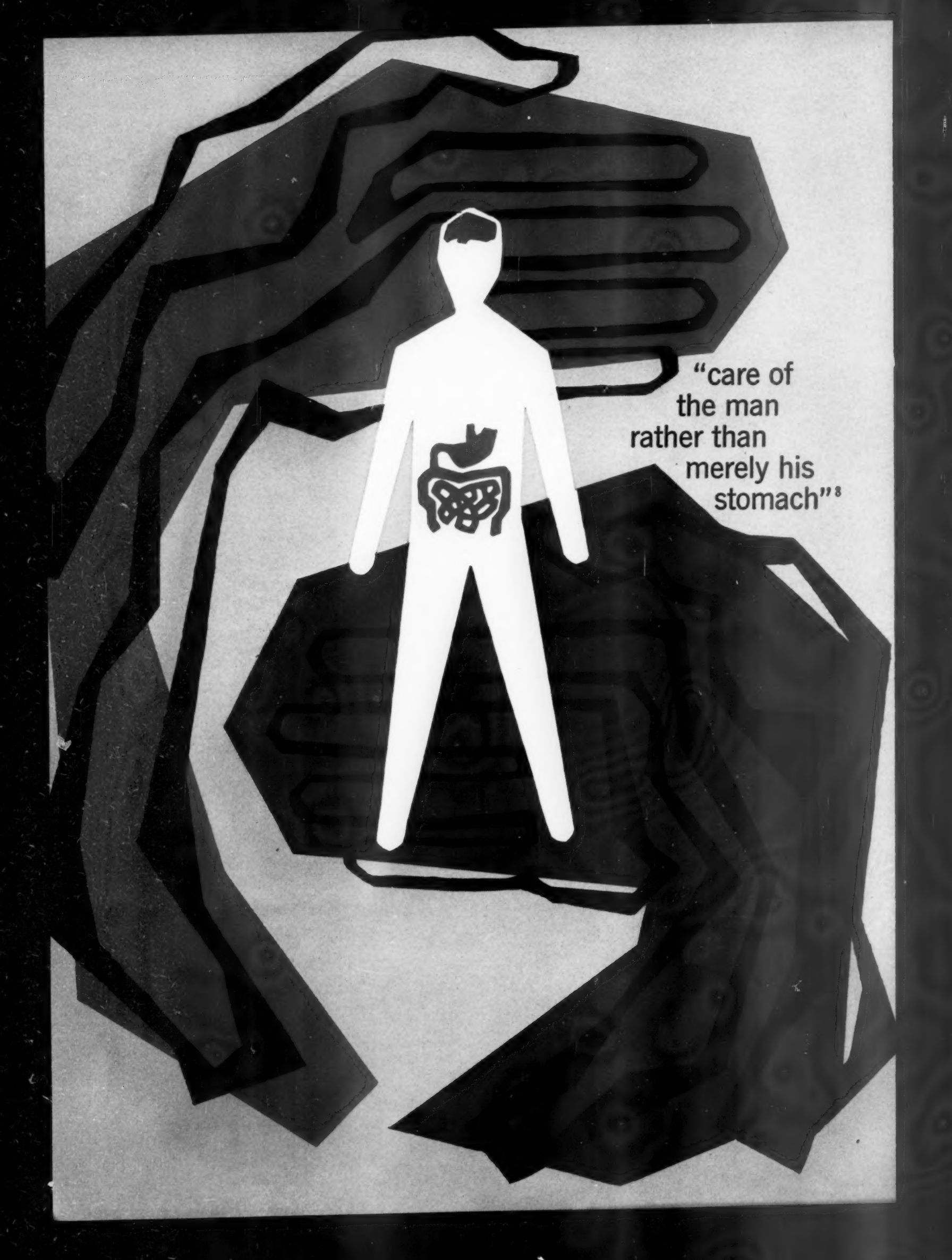
Sharp restriction of dietary salt appears indicated only in the presence of edema, but moderate restriction is usually recommended.

Lean meat is admirably suited for the diets prescribed in most forms of renal disease. It supplies relatively large amounts of high quality protein and only small amounts of sodium and chloride. Each 100 Gm. of unsalted cooked lean meat (except brined or smoked types) provides approximately 30 Gm. of protein, and only about 100 mg. of sodium and 75 mg. of chloride.

In addition to its nutritional contributions meat fulfills another advantageous purpose: It helps make meals attractive and tasty for the patient who must rigidly adhere to a restricted dietary regimen.


The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago . . . Members Throughout the United States



"care of
the man
rather than
merely his
stomach"⁸

"Milpath"

Miltown®  anticholinergic

two-level control of gastrointestinal dysfunction

at the central level

The tranquilizer Miltown® reduces anxiety and tension.^{1,3,6,7}

Unlike the barbiturates, it does not impair mental or physical efficiency.^{5,7}

at the peripheral level

The anticholinergic tridihexethyl iodide reduces hypermotility and hypersecretion.

Unlike the belladonna alkaloids, it rarely produces dry mouth or blurred vision.^{2,4}

indications: peptic ulcer, spastic and irritable colon, esophageal spasm, G. I. symptoms of anxiety states.

each "Milpath" tablet contains:

Miltown® (meprobamate WALLACE) 400 mg.
(2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate)

Tridihexethyl iodide 25 mg.
(3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethiodide)

dosage: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

available: bottles of 50 scored tablets.

references:

1. Altschul, A. and Billow, B.: The clinical use of meprobamate (Miltown®). *New York J. Med.* 57:2361, July 15, 1957. 2. Atwater, J. S.: The use of anticholinergic agents in peptic ulcer therapy. *J. M. A. Georgia* 45:421, Oct. 1956. 3. Borrus, J. C.: Study of effect of Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) on psychiatric states. *J. A. M. A.* 157:1596, April 30, 1955. 4. Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer. *Am. J. Digest. Dis.* 1:301, July 1956. 5. Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Experimental studies of behavioral effects of meprobamate on normal subjects. *Ann. New York Acad. Sc.* 67:701, May 9, 1957. 6. Phillips, R. E.: Use of meprobamate (Miltown®) for the treatment of emotional disorders. *Am. Pract. & Digest Treat.* 7:1573, Oct. 1956. 7. Selling, L. S.: A clinical study of Miltown®, a new tranquilizing agent. *J. Clin. & Exper. Psychopath.* 17:7, March 1956. 8. Wolf, S. and Wolff, H. G.: *Human Gastric Function*, Oxford University Press, New York, 1947.



WALLACE LABORATORIES
New Brunswick, N. J.

*Clinically tested in over 4,500 cases.**

Announcing a new
anorexigenic specific
not a CNS stimulant

"5 times safer (LD/50) than d-amphetamine"

 **LEVONOR***

(brand of 1-phenyl-2-aminopropane alginate,† Nordmark)

LEVONOR (1-phenyl, 2-aminopropane alginate, Nordmark) is a new anti-hunger compound that offers a sounder, more effective and more comfortable approach to weight reduction. It has proved remarkably successful in securing cooperation of patients on restricted diets.

LEVONOR...the appetite suppressant that can be given as late as 8 p.m.



does not interfere with sleep

In a study¹ of its effects on 173 overweight patients, "none of the patients complained of loss of sleep. In fact when 5 mg. of LEVONOR was given at 8 p.m. no interference with sleep was noted; night hunger was markedly diminished." This is a unique advantage since it is in the evening when most obese patients are tempted to break their diet.

no CNS overstimulation

LEVONOR has no effect on the mood of the patient. It does not overstimulate the cerebral cortex, thus avoiding jitteriness, tenseness, nervousness and disturbance of sleep.

depression of appetite is its primary effect

Unlike d-amphetamine, LEVONOR is *not* a central nervous system stimulant—its primary effect is to depress the appetite. Impressive results, even with late evening doses, are obtained without the addition of sedatives.¹⁻⁵

five times safer than dextro-amphetamine

LEVONOR's much greater safety (LD/50) and, concomitantly, its far greater freedom from side effects have been striking findings in extensive toxicity studies.¹

here are typical clinical results with LEVONOR:

STUDY NO. 1¹

Number of patients 173
Average daily dose . . . 2-3 tablets
(5 mg. each)
Average duration of
treatment 6 weeks
Average weekly weight
loss 2-2½ lbs.
Side effects 9*

*Minimized by dosage adjustment

STUDY NO. II²

Number of patients 52
Average daily dose . . . 2-3 tablets
(5 mg. each)
Average duration of
treatment 9 weeks
Average weekly weight
loss 2.1 lbs.
Side effects 1*

*Adjusted with dosage

economy and low dosage of LEVONOR make it possible to administer this drug long enough to favorably alter the patient's eating habits.

Administration and Dosage:

Average dose: 5 to 10 mg. twice daily.

Bibliography

1. Sc. Exhibit, N. Y. State Med. Meeting, Feb. 18-21, 1957.
2. Pomeranze, J.: Report 807: 1957.
3. Frohman, I. P.: Report 315: 1957.
4. Dwyer, Thomas: Report 912: 1957.
5. Gadek, R. J.: Report 186: 1957.
6. Sc. Exhibit, Mich. State Med. Soc. Meeting Sept. 25-27, 1957.

†Patent Pending °Trademark



NORDMARK Pharmaceutical Laboratories, Inc., Irvington, N. J.

among nonhormonal antiarthritics...

unexcelled in
therapeutic potency

BUTAZOLIDIN®

(phenylbutazone GEIGY)

In the nonhormonal treatment of arthritis and allied disorders no agent surpasses BUTAZOLIDIN in potency of action.

Its well-established advantages include remarkably prompt action, broad scope of usefulness, and no tendency to development of drug tolerance. Being nonhormonal, BUTAZOLIDIN causes no upset of normal endocrine balance.

BUTAZOLIDIN relieves pain, improves function, resolves inflammation in:

- Gouty Arthritis
- Rheumatoid Arthritis
- Rheumatoid Spondylitis
- Painful Shoulder Syndrome

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for detailed literature before instituting therapy.

BUTAZOLIDIN® (phenylbutazone GEIGY). Red coated tablets of 100 mg.

GEIGY

Ardaley, New York



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to prevent angina pectoris

Metamine®

Triethanolamine trinitrate biphosphate, LEEMING, 10 mg. *

Sustained

special advantages:

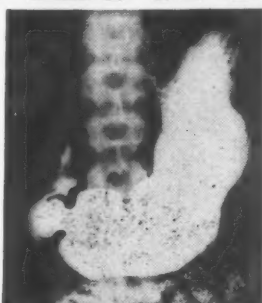
Simplified dose (b.i.d.)
No undesirable side reactions.
Greater economy.



Usual dose: 1 tablet on arising, 1 before evening meal. Bottles of 50 tablets.
THOS. LEEMING & Co., INC., New York 17, N. Y. *Patent applied for.

when anxiety and tension "erupts" in the G. I. tract...

IN DUODENAL ULCER



PATHIBAMATE*

Meproamate with PATHILON® Lederle

Combines Meproamate (400 mg.) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of duodenal ulcer — without fear of barbiturate loginess, hangover or habituation . . . *with* PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime. *Supplied:* Bottles of 100, 1,000.



*Trademark

• Registered Trademark for Tridihexethyl Iodide Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

outstanding
appetite
stimulant

INCREMIN*

LYSINE-VITAMIN SUPPLEMENT LEDERLE

Problem-eaters, the underweight, and generally below-par patients of all ages respond to INCREMIN.

INCREMIN offers L-Lysine for protein utilization, and essential vitamins noted for outstanding ability to stimulate appetite, overcome anorexia.

Specify INCREMIN in either Drops (cherry flavor) or Tablets (caramel flavor). Same formula. Tablets, highly palatable, may be orally dissolved, chewed, or swallowed. Drops, delicious, may be mixed with milk, milk formula, or other liquid; offered in 15 cc. polyethylene dropper bottle.

Each INCREMIN Tablet
or each cc. of INCREMIN Drops contains:

L-Lysine	300 mg.	Pyridoxine (B ₆)	5 mg.
Vitamin B ₁₂	25 mcgm.	(INCREMIN Drops contain	
Thiamine (B ₁)	10 mg.	1% alcohol)	


*Reg. U. S. Pat. Off.

Dosage only 1 INCREMIN TABLET or 10-20 INCREMIN Drops daily.

Lederle

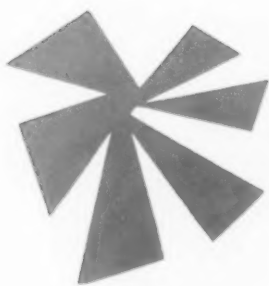
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AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK





new the
complete
cold formula

Antitussive
Antihistaminic
Decongestant
Analgesic-Antipyretic



ROMILAR CF



ROMILAR CF

The *new* complete cold formula

brings new ease and comfort to patients with colds and other upper respiratory disorders by providing more complete control of symptoms.

Each teaspoonful (5 cc) of pleasant tasting Romilar CF syrup provides:

ANTITUSSIVE	Romilar® Hydrobromide*	15 mg
ANTIHISTAMINIC	Phenylephrine Hydrochloride	5 mg
DECONGESTANT	Chlorpheniramine Maleate	1.25 mg
ANALGESIC-ANTIPYRETIC	N-acetyl-p-aminophenol	120 mg



Brand of dextromethorphan hydrobromide—the non-narcotic cough specific with codeine's antitussive effect but without codeine's side effects.

ROCHE LABORATORIES, Division of Hoffmann-La Roche Inc, Nutley, New Jersey

On Research Project CL19823:

Creating a major drug with great new promise*

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RAUDIXIN
TO RELIEVE
SOMATIC
SYMPTOMS**

*Elevated blood pressure
Increased pulse rate*



**RELY UPON
RAUDIXIN TO RELIEVE
PSYCHIC SYMPTOMS**

*Anxiety • Headache • Insomnia
Excitation • Tension • Agitation*

ACHIEVE TOTAL MANAGEMENT OF YOUR HYPERTENSIVE PATIENTS

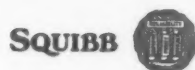
Raudixin helps you achieve total management of your hypertensive patients. Blood pressure is gently lowered. The work load of the heart is decreased. Psychic symptoms such as anxiety and tension are relieved. You can also use the smooth tranquilizing action of Raudixin on your tense and anxious normotensive patients. You will find that Raudixin has little, if any, effect on the blood pressures of such patients. Whole root rauwolfia (Raudixin) "is often preferred to reserpine in private practice, because of the additional activity of the whole root."* *Dosage:* Two 100 mg. tablets once daily; may be adjusted within a range of 50 to 300 mg. daily. *Supply:* 50 and 100 mg. tablets, bottles of 100, 1000 and 5000.

*Corrin, K. M.: Am. Pract. & Dig. Treatment 8:721 (May) 1957

PRESCRIBE RAUDIXIN

Squibb Whole Root Rauwolfia Serpentina

*RAUDIXIN® IS A SQUIBB TRADEMARK



Squibb Quality—the Priceless Ingredient

ACHROCIDIN is indicated for prompt control of undifferentiated upper respiratory infections in the presence of questionable middle ear, pulmonary, nephritic, or rheumatic signs; during respiratory epidemics; when bacterial complications are observed or expected from the patient's history.

Early potent therapy is provided against such threatening complications as sinusitis, adenitis, otitis, pneumonitis, lung abscess, nephritis, or rheumatic states.

Included in this versatile formula are recommended components for rapid relief of debilitating and annoying cold symptoms.

Adult dosage for ACHROCIDIN Tablets and new, caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children according to weight and age.

Available on prescription only

*symptomatic
relief... plus!*

ACHROCIDIN*

TETRACYCLINE-ANTIHISTAMINE-ANALGESIC COMPOUND

Tablets

Each tablet contains:

ACHROMYCIN® Tetracycline	125 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Salicylamide	150 mg.
Chlorothen Citrate	25 mg.

Syrup

Each teaspoonful (5 cc.) contains:

ACHROMYCIN® Tetracycline equivalent to tetracycline HCl	125 mg.
Phenacetin	120 mg.
Salicylamide	150 mg.
Ascorbic Acid (C)	25 mg.
Pyridamine Maleate	15 mg.
Methylparaben	4 mg.
Propylparaben	1 mg.



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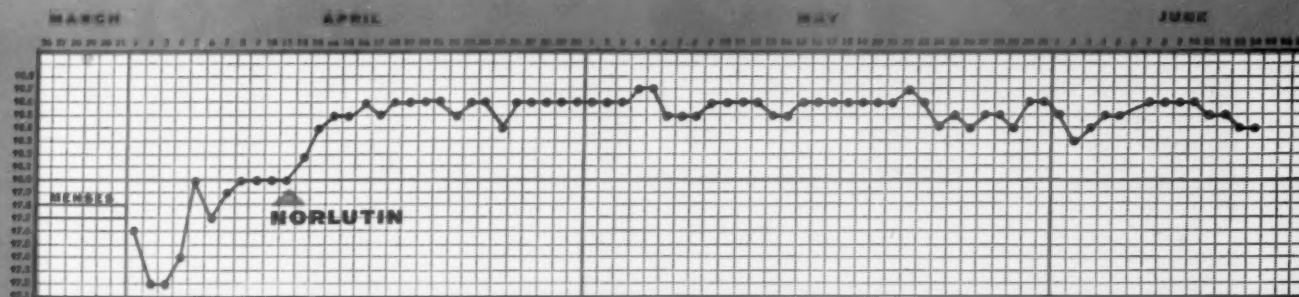
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oral progestational agent
with
unexcelled potency
and
unsurpassed efficacy

With NORLUTIN you can now prescribe truly effective *oral* progestational therapy. Small oral doses of this new and distinctive progestogen produce the biologic effects of injected progesterone.

THERMOGENIC EFFECT



▲ When NORLUTIN was administered to patients with uniphasic temperature curves and menstrual irregularities a rise in basal temperature occurred.*

NORLUTINTM

(norethindrone, Parke-Davis)

major advance in female hormone therapy
for certain disorders
of menstruation and pregnancy

INDICATIONS FOR NORLUTIN: conditions involving deficiency of progestogen, such as primary and secondary amenorrhea, menstrual irregularity, functional uterine bleeding, endocrine infertility, habitual abortion, threatened abortion, premenstrual tension, and dysmenorrhea.

PACKAGING: 5-mg. scored tablets (C. T. No. 882), bottles of 30.

*Greenblatt, R. B.: *J. Clin. Endocrinol.* 16:869, 1956.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN



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Now...victory over infections

- **pharmacodynamically superior**
- **therapeutically unsurpassed**

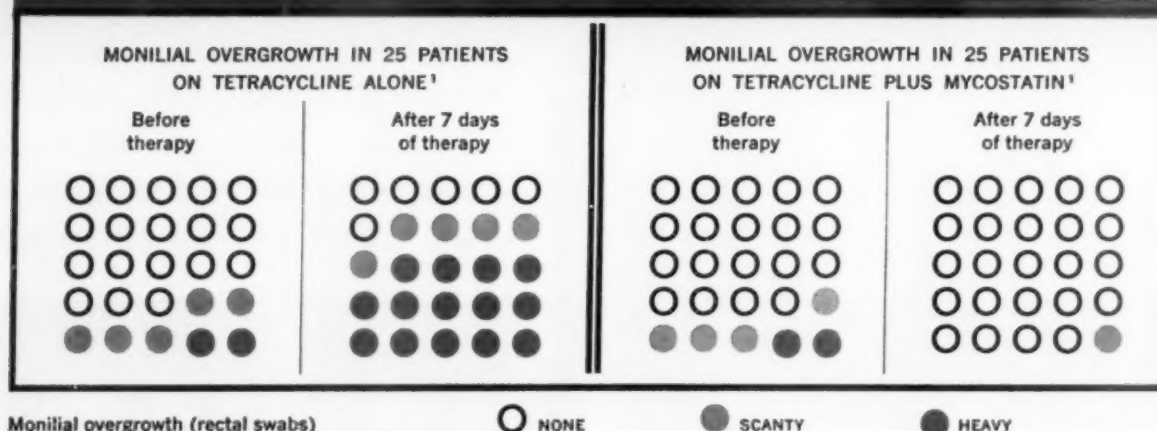
With Mysteclin-V you get faster and greater absorption of tetracycline than ever attainable in the past . . . providing all the benefits of well-established tetracycline therapy.

For practical purposes, Mysteclin-V is sodium-free.

MYSTECLIN-V

Spectra-Tetracycline Phosphate Complex (Bismuth) and Mycostatin (nystatin)

Contains Mycostatin to forestall monilial overgrowth and possible complications



Mycostatin in Mysteclin-V prevents gastrointestinal monilial overgrowth, thereby minimizing the possibility of antibiotic-induced monilial superinfection.

Supply	Tetracycline phosphate complex, equiv. to tetracycline HCl (mg.)	Mycostatin (units)	Packaging
Capsules (per capsule)	250	250,000	Bottles of 16 and 100
Half-Strength Capsules (per capsule)	125	125,000	Bottles of 16 and 100
Suspension (per 5 cc.)	125	125,000	2 oz. bottles
Pediatric Drops per cc.—20 drops	100	100,000	10 cc. bottles with dropper

1. Childs, A. J.: British M. J. 1:660 (March) 1956.

SQUIBB  **Squibb Quality—the Priceless Ingredient**

*MYSTECLIN®, *BISMUTHIN® and *MYCOSTATIN® ARE SQUIBB TRADEMARKS

in menopausal turmoil

THEELIN R-P*

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• prolonged action for continuing need

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PSORIASIS

*Proved Clinically Effective Oral Therapy —
maintenance regimen may keep patients
lesion-free.*

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LIPAN Capsules contain: Specially prepared highly activated, desiccated and defatted *whole* Pancreas: Thiamin HCl, 1.5 mg. Vitamin D, 500 I.U.

Available: Bottles 180's, 500's.

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effective, selective therapy

Cantil

for the colon

for functional and organic disorders

CANTIL relieves pain, cramps, bloating...curbs diarrhea...restores normal tone and motility. Selective action focused on the colon avoids widespread interference with normal autonomic function...minimizes urinary retention, mouth dryness, blurring of vision.

HOW CANTIL IS PRESCRIBED One or two tablets three times a day preferably with meals, and one or two tablets at bedtime for patients with ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

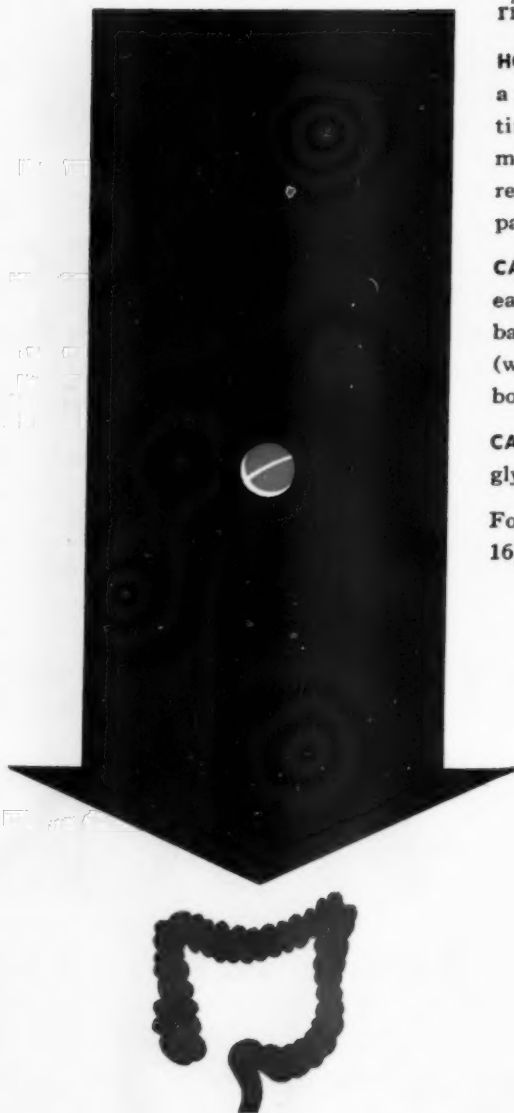
CANTIL—TWO FORMS CANTIL (plain)—25 mg. of CANTIL in each scored tablet—bottles of 100. CANTIL with Phenobarbital—25 mg. of CANTIL and 16 mg. of phenobarbital (warning: may be habit forming) in each scored tablet—bottles of 100.

CANTIL is the *only* brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

For more detailed information, request Brochure No. NDA 16, Lakeside Laboratories, Milwaukee 1, Wisconsin.

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14457





On Research Project CL19823:

Creating a major drug with great new promise*

*Coming soon from

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

rational adjunct to tranquilizing therapy

According to Campbell the more tense the patient and the longer the duration of his anxiety, the greater will be the nutritive requirements.¹

STRESSCAPS replenish the specific vitamin losses sustained by tense, anxious patients, increasing their resilience to stress situations. STRESSCAPS provide generous amounts of B-vitamins and vitamin C in a professionally accepted formulation.

Each Capsule Contains:

Thiamine Mononitrate (B ₁)	10 mg.
Riboflavin (B ₂)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B ₆)	2 mg.
Vitamin B ₁₂	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average Dose: 1-2 capsules daily.

1. Campbell, D. G.: In: *Modern Nutrition in Health and Disease*, Wohl, G. M. and Goodhart, R. S. (Editors), Lea & Febiger, Philadelphia, 1955, p. 814.

STRESSCAPS in STRESS

• Infection • Physiologic Trauma • Endocrine Dysfunction • Emotional Stress • Pre- and Postoperatively*

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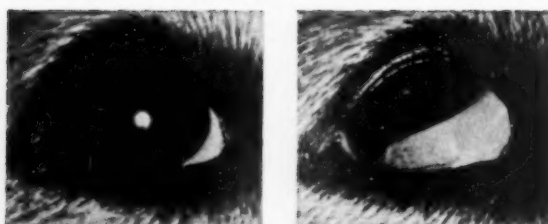
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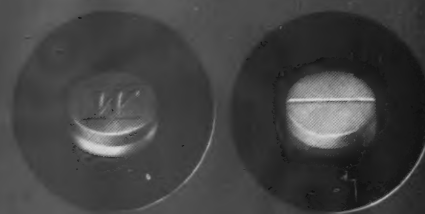
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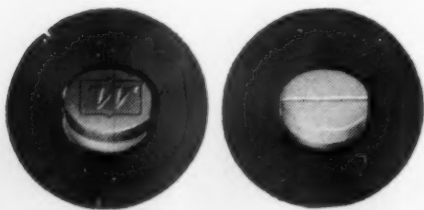


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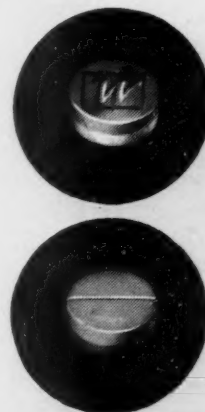
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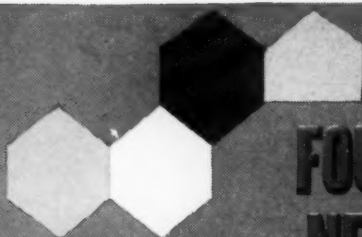
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references (1) Settel, E.: Am. Pract. & Digest Treat. 8:443, 1957. (2) Johnson, H. J., Jr.: Am. Pract. & Digest Treat., in press. (3) Council on Pharmacy and Chemistry, A.M.A.: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1957, p. 508.

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1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, American Medical Association Meeting, New York, June 3-5, 1957.

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1. Goodman, L. S. and Gilman, A.: *The Pharmacological Basis of Therapeutics*, Ed. 2, The Macmillan Co., New York, 1955, p. 856.

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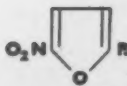
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1. Maynert, E. W. and Losin, L.: J. Pharmacol. & Exper. Therap. 115:275-282 (Nov.) 1955.

2. Butler, T. C. et al.: J. Pharmacol. & Exper. Therap. 111:425 (Aug.) 1954.

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†Cohen, B. M.; Cross, E. B., and Johnson, W.: Am. Pract. & Digest Treat. 6:1030, 1955

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Bibliography. Orgain, E. S.: Postgrad. Med. 17:318, 1955. Finnerty, F. A.: Am. J. Med. 17:629, 1954. McCall, N. L.; Sass, D. K.; Wagstaff, C., and Cutler, J.: Obst. and Gynec. 6:297, 1955. Cohen, B. M.: New York State J. Med. 55:653, 1955. La Barbera, J. F.: Med. Rec. and Annals 50:242, 1956. Voskian, J.; Assali, N. S., and Noll, L.: Surg., Gynec. and Obst. 102:37, 1956. Crisp, W. E., and McCall, M. L.: Am. Pract. and Digest Treat. 7:620, 1956. Finnerty, F. A.: Am. J. M. Sc. 229:379, 1955.



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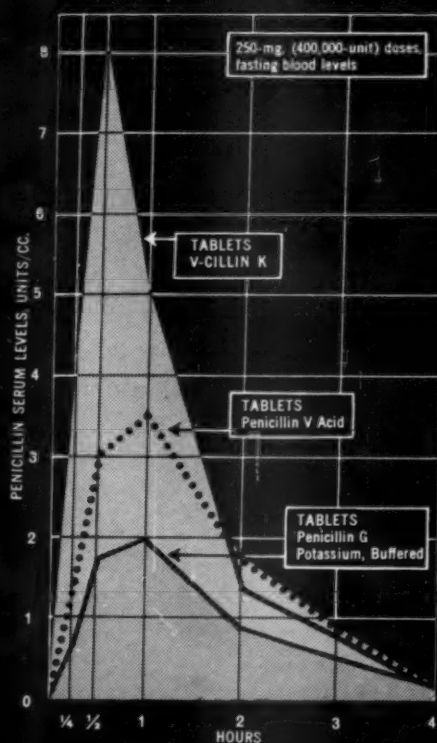
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VOL. XXIII

DECEMBER, 1957

No. 6

Editorial

Drug Reactions Characterized by Cholestasis Associated with Intrahepatic Biliary Tract Obstruction

MINOR degrees of drug hepatotoxicity may occur without overt manifestations and are detectable, if at all, only by slight abnormalities in liver function tests or in the hepatic structure observed at liver biopsy. More severe hepatotoxicity, with the appearance of jaundice, usually is characterized by liver cell necrosis. However, the jaundice due to certain drugs, often after relatively low dosage, is accompanied by little or no morphological indication of liver cell damage but is instead associated with striking bile stasis in the finer radicles of the intrahepatic biliary tract. This histologic picture and the concurrent functional derangement closely mimic the findings in jaundice due to mechanical obstruction of the extrahepatic biliary tract, of which direct examination, however, gives no indication. Indeed, differentiation from "surgical jaundice" may be so difficult, particularly if pain in the right upper quadrant is present and a history of prior drug administration is overlooked, that abdominal exploration may be undertaken because of mistaken or uncertain diagnosis.

The proximate mechanisms of this interesting form of obstructive jaundice are still obscure. They have taken on added interest recently because of the not infrequent occurrence of this type of drug reaction after administration of the widely dispensed drug, chlorpromazine (thorazine,[®] largactil[®]).

Postarsphenamine Jaundice. This peculiar expression of drug hypersensitivity appears to have been first described in 1940, in relation to arsphenamine [7]. Twelve cases of postarsphenamine jaundice were reported which could be differentiated from the more common arsenical-induced hepatocellular injury, and from infectious hepatitis now known to be caused by syringe-transferred SH virus, by the following characteristics: (1) Acute onset with prodromal systemic symptoms (fever, malaise, headache, anorexia, nausea and vomiting, usually associated with allergic manifestations such as skin rash, arthralgias, chemosis, and eosinophilia) coming on several hours after the second or third intravenous arsenical injection, i.e., in the initial week or two of antisyphilitic therapy. (2) Appearance within several days of painless jaundice which was apt to persist for weeks or months, accompanied by pruritus, dark urine and light stools. (3) Laboratory criteria of biliary tract obstruction with little or no indication of hepatocellular damage: increased serum alkaline phosphatase levels (mostly in the range of 20 to 40 Bodansky units per 100 cc.), usually negative cephalin flocculation tests, and frequently elevated serum cholesterol (300 to 500 or more mg. per 100 cc.). The possibility of extrahepatic biliary tract obstruction was excluded in three cases by surgical exploration. (4) Preservation of essentially normal liver parenchyma

in liver biopsies, the principal lesions being bile stasis in the finer biliary radicles, with "cholangiolitis," "pericholangitis" and inflammatory cell infiltration (including eosinophils in some cases) in the portal areas. (5) Eventual recovery of the patient.

Drug hypersensitivity was suggested [7] as the cause of this syndrome in view of the high general incidence of allergic reactions to arsphenamine, the low total dosage of arsenic administered, the acute onset after the second or third injection of the drug, the association with frankly allergic phenomena, and the accelerated recurrence of severe symptoms when the arsenical was readministered.

Similar Reactions to Other Drugs. Of the many drugs causing analogous reactions in susceptible persons, chlorpromazine produces the most closely related syndrome, with conspicuous cholestasis and little or no evidence of hepatocellular damage. The others include dinitrophenol [7], cinchophen [2], aurothioglucose [2], methyltestosterone [3,4], norethandrolone (Nilevar) [5], thiouracil [6], para-aminosalicylic acid [7], sulfadiazine [8], methimazole [9] and 8-(para-aminobenzyl) caffeine [10]. Popper [11] has discussed the variations in the histological abnormalities of the intrahepatic biliary tract and hepatic parenchyma produced by these agents. Toluylene diamine may cause obstruction of the intrahepatic biliary tract but this blockage is a consequence of intense hemolysis [7].

It is well known that viral hepatitis may manifest itself as intrahepatic obstructive jaundice with pronounced cholestasis, periportal infiltration and minimal hepatocellular necrosis (Eppinger's "periacinar or cholangitic form of catarrhal jaundice" [12]; the "cholangiolitic type" of Watson and Hoffbauer [13]). The characteristics of this disorder have been discussed at some length by Popper [11] and Johnson and Doenges [14].

Chlorpromazine Jaundice. The first reports of icterus complicating chlorpromazine therapy appeared in 1954. In that year also, Zatuchni and Miller [15], on the basis of clinical, chemical and histologic similarities, classified chlorpromazine jaundice with the drug hypersensitivity reactions characterized by cholestasis associated with intrahepatic biliary tract obstruction. This view has won general acceptance [16-20, and others].

The current proportions of the problem pre-

sented by chlorpromazine jaundice are indicated by data collected by the Smith, Kline & French Laboratories (cited by Hollister [20]). These reveal an over-all incidence of overt jaundice of 1 to 2 per cent in patients treated with the drug for at least one week, a figure which does not take into account the occurrence of hepatotoxicity not accompanied by manifest icterus. Of some four million patients who have received chlorpromazine, jaundice has been recorded in 880. There have been thirteen deaths attributable to the drug.

The clinical course of chlorpromazine jaundice is exemplified by that of twenty-two patients observed at The Mount Sinai Hospital, recently reported in some detail by Werther and Korelitz [19]. The average total dose given (orally) to these patients was 1,260 mg. Prodromal symptoms, appearing at a mean of fourteen days after beginning chlorpromazine therapy and lasting a mean of 4.5 days, included (in order of frequency) fever, pain in the epigastric region or in the right upper quadrant, chills, nausea, vomiting, myalgias, lassitude, maculopapular skin eruption. Eosinophilia was usually present. Jaundice developed after an average interval of 18.6 days from the start of chlorpromazine therapy and was usually preceded and accompanied by pruritus, dark urine and light stools. The highest bilirubinemia recorded was 14.8 mg. per cent. That the jaundice was due to biliary tract obstruction was evident from elevated serum alkaline phosphatase levels (up to 36.4 King-Armstrong units) in twenty-one of the twenty-two cases, negative cephalin flocculation tests in all but two cases, and a serum total cholesterol greater than 300 mg. per cent (maximum 406 mg. per cent) in eight of the sixteen patients tested. The average duration of jaundice was thirty days (range, seven to 122 days) and recovery was uneventful in every instance. One patient was subjected to futile surgical exploration to exclude extrahepatic biliary tract obstruction. Liver biopsy in six cases showed the characteristic cholestasis and periportal inflammatory cell infiltration, which in three instances examined relatively early in the course included many eosinophils; evidence of centrilobular liver cell regeneration was noted in four of the biopsies.

There is every indication that chlorpromazine jaundice, like arsphenamine jaundice of the obstructive type, is an expression of drug hypersensitivity. Chlorpromazine is notoriously prone

to produce other hypersensitivity reactions, including drug fever, urticaria, angioneurotic edema, maculopapular eruption, erythema multiforme, exfoliative dermatitis, contact dermatitis, photosensitivity, asthma and agranulocytosis. The early onset of jaundice, sometimes after very small total dosage of the drug [21,22], suggests drug hypersensitivity. This interpretation is further supported by the frequent association with prodromal systemic symptoms that may be overtly allergic, the prevalence of eosinophils in the peripheral blood and hepatic portal areas in the earlier phases of the reaction, and—although this is not a universal experience—the results of challenge tests. Hollister [20] reports recurrence of overt jaundice in six of eleven patients who were given challenge doses of 100 to 300 mg. chlorpromazine for a day or two as long as seventeen months after their initial attack of chlorpromazine jaundice; in three others chemical indications of biliary tract obstruction developed without jaundice. Challenge with promazine, which differs from chlorpromazine only in the absence of the chlorine substitution in position 2, did not produce jaundice, i.e., there was no apparent cross-sensitization.

Pathogenesis of Obstructive Jaundice Due to Drug Hypersensitivity. The distinguishing manifestations of this form of drug reaction are those characteristic of biliary tract obstruction, typically with overt jaundice, in association with free extrahepatic biliary channels and substantially normal hepatocellular morphology. It is therefore inferred, justifiably, that the causal agent must act somewhere within the intrahepatic biliary radicles, presumably at or distal to the bile capillaries, which are the seat of cholestasis. Whether the cholestasis is the cause or a result of the intrahepatic biliary tract obstruction is not altogether clear. It has been variously conjectured that the stasis of bile may be due to direct chemical injury to the cholangioles with inflammatory response ("cholangiolitis"); a direct action of the noxious agent on the bile, increasing its viscosity; abnormal permeability or rupture of the cholangioles with loss of water and consequent inspissation of the bile; compression of the bile capillaries by swollen hepatic cells; or other alteration. There is some indication that even in cases with seemingly intact liver parenchymal structure and function there may be specific derangements of the hepatic cells. This is suggested, for example, by elevated serum glutamic-oxaloacetic trans-

aminase levels [23] and occasional centrilobular necrosis.

In respect to postarsphenamine jaundice of the obstructive type, it was surmised [7] that the selective injury to the finer biliary radicles might be the result of abnormal release into the bile of the colloidal parent drug or a toxic metabolite ordinarily held and degraded by the Kupffer or hepatic cells. It is possible that some such metabolic defect is responsible for chlorpromazine jaundice. Chlorpromazine (2-chloro-10-(3-dimethylaminopropyl) phenothiazine hydrochloride) is distributed, after injection or ingestion, chiefly to the brain, lungs, spleen, kidneys and liver, according to Salzman and Brodie [24]. It occurs in the plasma very largely in protein-bound form. The urinary excretion of the drug, as such, is negligible but there is significant excretion in the bile [20]. Chlorpromazine is rapidly metabolized by the homogenized rabbit liver [24]; it is in large part first oxidized to the sulfoxide (apparently by peroxidases and catalase, according to Cavanaugh [25]), then further degraded to a number of unidentified products.

Complications of Obstructive Jaundice Due to Drug Hypersensitivity. Uneventful and apparently complete recovery is the rule but occasionally the course may be prolonged for many weeks or months. Death in thirteen cases has already been noted.

An unusual but particularly significant sequence of events is the (rare) development of xanthomatous biliary cirrhosis associated with marked elevation of the serum cholesterol. In two of the initial series of cases of postarsphenamine jaundice of the obstructive type [7] the serum cholesterol gradually rose to levels in excess of 1,000 and 3,000 mg. per cent, respectively, without the appearance of xanthomata; the comment was made that "for reasons not apparent the upward trend in serum cholesterol levels usually became more marked in the recovery phase of illness, when the serum bilirubin values began to fall." Three cases of postarsphenamine jaundice have been described [26-28] in which marked hypercholesterolemia was sustained and xanthomatosis developed ten months to more than two years after administration of the drug. The patient described by Stolzer et al. [28] was still jaundiced (seventeen months) and xanthomatous (eight months) at the time of publication, with liver biopsy findings of biliary cirrhosis of the peri-

cholangiolitic type, and marked cholestasis; the final outcome is not known. The others eventually recovered spontaneously.

Similar complications may result as a consequence of chlorpromazine jaundice. Myers and his associates [29] have recently given a detailed description of such a case, in which extensive xanthomata appeared about five months after onset of jaundice, associated with hyperlipemia, serum cholesterol levels as high as 2500 mg. per cent, and remarkably increased levels of prothrombin, proconvertin and proaccelerin. Studies with acetate-1-C¹⁴ at this time indicated enhanced biosynthesis of cholesterol and phospholipid, in addition to presumptive biliary retention. About thirteen months after onset, the hyperlipoidemia and xanthomatosis began spontaneously to decrease and finally disappeared completely. Liver biopsies, which showed the typical picture of cholestasis and xanthomatous biliary cirrhosis at the height of the disorder, subsequently revealed increasing portal fibrosis as the major anomaly.

These curious late complications, the mechanisms of which are quite obscure, emphasize some of the potential hazards of indiscriminate administration of drugs prone to elicit a cholestatic reaction in the liver. It would appear that portal fibrosis of the liver may eventually ensue, perhaps changes indicative of biliary cirrhosis [30]. One wonders whether "primary biliary cirrhosis" [31] may occasionally arise from such cause.

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Clinical Studies

Splenic Venography and Intrasplenic Pressure Measurement in the Clinical Investigation of the Portal Venous System*

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THE clinical application of transplenic portal venography followed the demonstration in 1951 by Abeatici and Campi [1] that the portal system could be outlined radiologically in the dog by the injection of contrast medium into the spleen, and the first percutaneous transplenic venogram in man was done in the same year by Boulvin, Chevalier, Gallus and Nagel [2]. Many papers have appeared since then [3-9] and sufficient knowledge has now accumulated to permit evaluation of the technic and the indications for its use.

Atkinson and Sherlock [10] showed that the portal venous pressure could be determined from the pressure in the splenic pulp, which is in free communication with radicles of the splenic vein. The present communication discusses the clinical applications of percutaneous splenic venography and intrasplenic pressure measurement.

METHODS

The technics of measurement of the intrasplenic pressure and splenic venography have been fully described previously [6,8,10]. The two procedures were

usually carried out consecutively with the patient on the x-ray table, but in some instances measurement of the splenic pressure was carried out as a separate bedside procedure. The intrasplenic pressure was measured through a fine needle connected by a length of polythene tubing to a strain gauge and photographic recording galvanometer. The polythene tubing allowed free movement of the needle with respiration. The pressure was measured in at least two positions in the splenic pulp, and the final figure calculated as the mean of the readings obtained, taking the zero level as 5 cm. below the sternal angle with the patient in a supine position. In most instances there was very little fluctuation in the pressure record with shallow respiration or cardiac systole (Fig. 1), and there was close agreement between the pressure recorded at different sites in the spleen. (Fig. 2.) Occasionally the needle tip lay in or near a branch of the splenic artery, whereupon a typical pulsating record was produced; these tracings were discarded. The mean normal intrasplenic pressure was found to be 8 mm. Hg (standard deviation, 4).

Splenic venography was carried out by injecting diodone® into the spleen through a needle, 0.75 mm. in external diameter and 7 cm. in length. The needle was connected by a pressure-tight screw to polythene

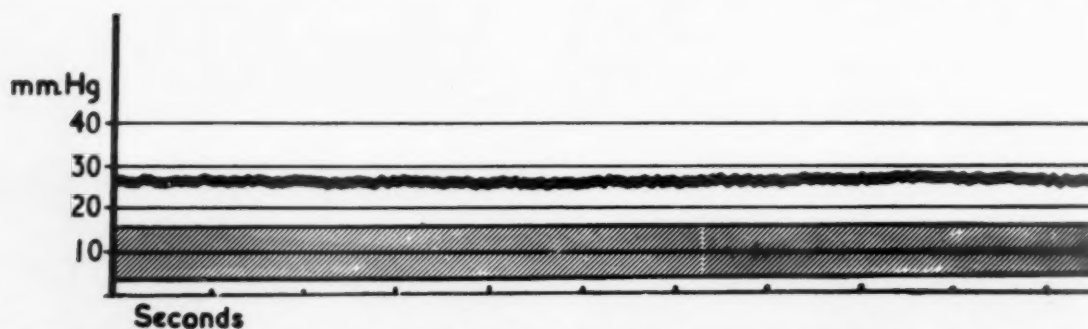


FIG. 1. Intrasplenic pressure record, portal hypertension due to cirrhosis. Little change in pressure with cardiac systole or shallow breathing. Hatched area is normal range of intrasplenic pressure.

* From the Departments of Medicine and Radiology, Postgraduate Medical School, University of London.

tubing leading to the pressure injection apparatus. In an adult, 40 ml. of diodone was injected in eight to ten seconds. A series of films was taken, commencing after two-thirds of the contrast medium had been administered. Thirty-nine investigations were carried out on a Schonander biplane serial angiographic table and the remaining eighty-seven on a simple manually-operated cassette tunnel. Two 12 by 12 inch films were exposed synchronously in the lateral and antero-posterior planes on the Schonander table, a total of ten films in each plane being taken in seven seconds. With the cassette tunnel, five 15 by 12 inch antero-posterior films were taken in ten to twelve seconds.

CONTRAINDICATIONS

Splenic puncture should not be performed if there is clinical evidence of a bleeding tendency, if the one-stage prothrombin time exceeds the control time by 50 per cent, or if the platelet count is less than 100,000/cu. mm. Jaundice is a contraindication even with a normal prothrombin time. In the presence of ascites, paracentesis should precede venography. Diodone sensitivity contraindicates venography unless desensitisation is possible [17]; an intravenous test dose of 1 to 2 ml. of diodone is always administered. An impalpable spleen is not a contraindication to venography, as the point for insertion of the needle can be determined by percussion and provided care is taken to see that blood flows freely from the needle before the diodone is injected, satisfactory venograms can be obtained. When the spleen is not large it is sometimes useful to place an opaque marker on the abdomen at the level of the point chosen for the injection before the preliminary film is taken.

VENOGRAPHIC APPEARANCES

One hundred and twenty-six venograms were obtained in 109 patients (Table 1); seventy-three patients suffered from hepatic cirrhosis of the portal or postnecrotic type, ten from biliary cirrhosis and twelve from extrahepatic portal vein obstruction without cirrhosis. A miscellaneous group of fourteen patients comprised three with Gaucher's disease, two with haemochromatosis, two with fatty livers, one with Hodgkin's disease, one with haemolytic anaemia, one with a primary malignant hepatoma without cirrhosis, one with a hepatic haemangioma, one with chronic pancreatitis, one with myelofibrosis and one with undiagnosed splenomegaly.

In the normal venogram only the splenic vein and the portal vein with its intrahepatic

branches are filled. A filling defect may be seen in the portal vein where the superior mesenteric blood joins that of the splenic vein; this streaming rarely extends as far as the porta hepatis [12]. There is considerable variation in the size and direction of the normal splenic and

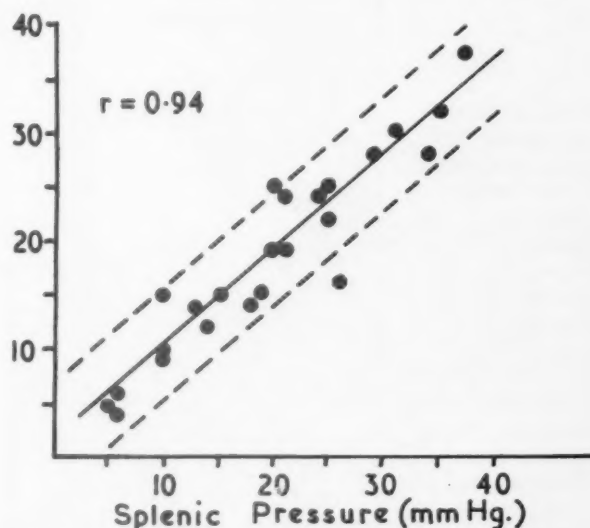


FIG. 2. The relation between the pressure recorded at two different sites in the same spleen. Ordinate represents pressure at one point and abscissa pressure at another point. Solid line is the calculated regression line for the points shown and the interrupted lines the 95 per cent confidence limits (r = correlation coefficient).

portal veins. The intrahepatic part of the portal vein shows an even branching and reduction in calibre, and both lobes of the liver are outlined; the right however, more than the left. The hepatic veins are seen only very rarely in the later films.

In portal cirrhosis the appearance of the venogram is very variable. On the one hand it may be entirely normal, and on the other may show numerous collateral channels. (Fig. 3.) Three of the ten patients with biliary cirrhosis showed a portal collateral circulation. One patient with haemochromatosis had an extensive gastro-oesophageal circulation.

In most patients with extrahepatic portal vein obstruction no contrast medium enters the portal vein and the characteristic feature is the large collateral circulation arising from the spleen or splenic vein. In two patients a paraportal circulation around a local block was present and in one patient, with a localised obstruction at the porta hepatis, the venogram demonstrated a sufficient length of portal vein for a subsequent successful portacaval anastomosis.

TABLE 1
INDICATIONS FOR 126 SPLENIC VENOGRAMS OBTAINED IN 109 PATIENTS

Diagnosis	No. of Patients	No. of Venograms		Indications					
		Suc- cessful	Failed	Gastro- intestinal Bleeding	Enlarged Spleen	Enlarged Liver	P-S E*	Ascites	Other
'Portal' cirrhosis.....	73	79	9	43	8	2	20	..	15
Extrahepatic portal vein occlusion.....	12	13	..	8	2	3	..
Primary biliary cirrhosis.....	7	6	1	5	..	1	1
"Secondary biliary cirrhosis".....	3	4	..	2	2
Gaucher's disease.....	3	3	..	1	2
Hemochromatosis.....	2	2	..	1	1
Fatty liver.....	2	1	1	2
Hodgkin's disease.....	1	..	1	..	1
Acquired hemolytic anaemia.....	1	..	1	..	1
Hepatoma.....	1	1	1
Hemangioma.....	1	1	1
Chronic pancreatitis...	1	..	1	..	1
Myelosclerosis.....	1	1	..	1
Undiagnosed splenomegaly.....	1	1	1
Total.....	109	112	14	61	16	7	20	3	19

NOTE: In some instances the final diagnosis was reached only after the performance of the venogram.

* P-S E = Portal = systemic encephalopathy (episodic stupor).

† Other (indications) include the postoperative investigation of portacaval anastomoses, the investigation of suspected pancreatic lesions and of hepatomas.

The three patients with Gaucher's disease had splenomegaly with large tortuous splenic veins, but no collaterals were filled.

COMPLICATIONS

Complications from intrasplenic pressure measurement and splenic venography were unusual. There were occasional complaints of slight discomfort in the splenic region for a few minutes after the injection. Within ten to fifteen seconds after the end of the injection many patients flushed, complained of feeling hot and of a taste in the mouth.

Three patients suffered from pain in the left upper abdominal quadrant for several hours although there was no radiologic evidence of extravasation of diodone. In six patients the bulk of diodone was injected into the peritoneal cavity, producing severe pain lasting for some twenty minutes but without further ill effect. The portal system was not outlined in four patients,

but in the other two some diodone entered the portal vein, giving a venogram. Extravasation was always due to superficial injection of diodone as the length of the needle is such that it is virtually impossible to push it right through an enlarged spleen. The importance of relatively deep injection of diodone has also been stressed by Bergstrand and Ekman [13].

In one patient, the first in the series, diodone was injected into the colon without ill effect. This complication has also been reported by others [5,14].

Slight intraperitoneal bleeding is probably usual after splenic puncture and small amounts of blood have been found in the peritoneal cavity when laparotomy is performed shortly after venography [15]. O'Sullivan and Evans [16] operated upon eighteen patients within minutes of splenic venography and found that haemorrhage had ceased in all but one, a patient with thrombocytopenia.

The slight haemorrhage probably accounts for the transient upper abdominal discomfort experienced by some patients, but clinically obvious intraperitoneal haemorrhage was observed on only four occasions. Two patients with portal cirrhosis had mild shock and abdominal pain within three hours of simple splenic pressure measurement without venography. Two other patients, one suffering from biliary and the other from portal cirrhosis, showed clinical signs of intraperitoneal haemorrhage two hours and five days, respectively, after combined intrasplenic pressure measurement and venography. These four patients received blood transfusions but in no instance was splenectomy necessary and all recovered uneventfully.

Three patients with portal cirrhosis and oesophageal varices had haematemesis within thirty-six hours of venography. Two patients had previously suffered from gastrointestinal haemorrhage and transfusion was not necessary. The third patient, who had never bled previously, had a severe haematemesis and recovered after blood transfusion and the insertion of a Sengstaken [17,18] oesophageal compression tube.

In two patients mild urticaria developed one hour after the injection, without other evidence of diodone sensitivity, and in both the rash cleared rapidly with antihistaminics.

FAILURES

Fourteen of 126 venograms were technical failures (Table 1), usually from a breakdown in the x-ray apparatus. In four patients insufficient contrast medium entered the spleen to produce a picture of the portal system. On one occasion no blood could be obtained from the needle hilt and, although the tip seemed to be in the spleen, diodone was not injected.

INDICATIONS FOR SPLENIC VENOGRAPHY

The major indications for splenic venography were gastrointestinal haemorrhage, undiagnosed splenomegaly and hepatomegaly, neuropsychiatric changes in patients with liver disease, suspected hepatic tumours and ascites of obscure aetiology. (Table 1.)

Gastrointestinal Haemorrhage and Suspected Portal Hypertension. Gastrointestinal haemorrhage is the most important indication for splenic venography which may be of use in determining both the cause of the bleeding and its clinical management.

Diagnosis: Peptic ulceration is commonly associated with cirrhosis of the liver [19], and gastrointestinal haemorrhage in a patient with chronic liver disease may arise not only from oesophageal varices but from a peptic ulcer. If portal venography fails to show a gastro-

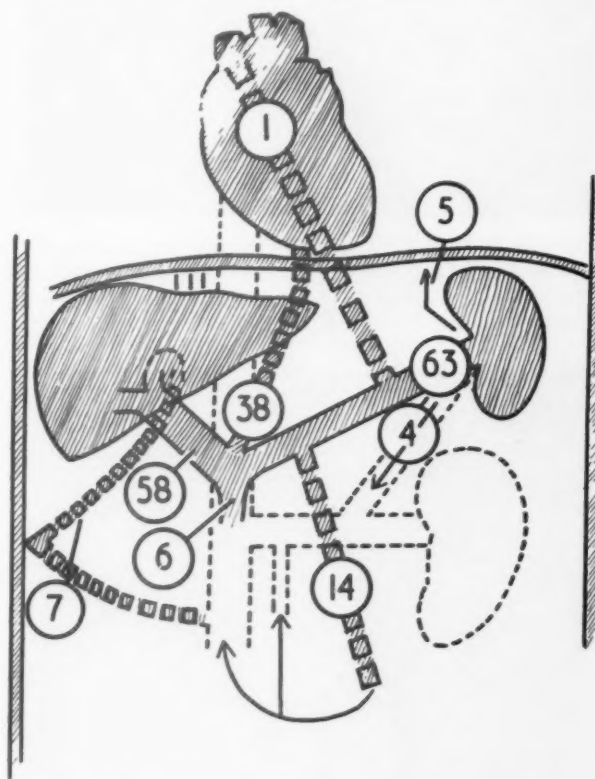


FIG. 3. The vessels shown in sixty-three venograms of patients with cirrhosis. The splenic vein was outlined in all sixty-three patients, the portal in fifty-eight, gastric and oesophageal vessels in thirty-eight, the inferior mesenteric in fourteen, some of these having a return of diodone to the inferior vena cava through the ovarian or testicular vein; umbilical veins filled in seven, there was slight reflux into the terminal part of the superior mesenteric vein in six, veins between spleen and diaphragm filled in five, and between spleen and renal vein in four. In one patient the majority of the injected diodone entered the azygos system.

oesophageal collateral circulation, bleeding from varices is most unlikely. The presence of an extensive oesophageal collateral circulation is strong though not conclusive evidence that varices are the source of the bleeding.

CASE 1. A forty-five year old housewife had suffered some years of intermittent dyspepsia with several episodes of haematemesis and melaena. The liver and spleen were enlarged and numerous spider naevi were present. Routine liver function tests suggested portal cirrhosis and this was confirmed by liver

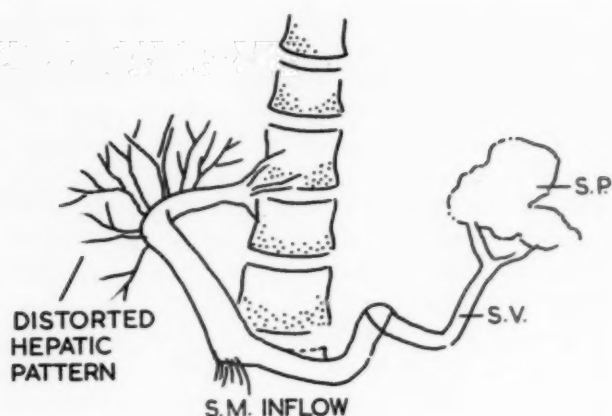
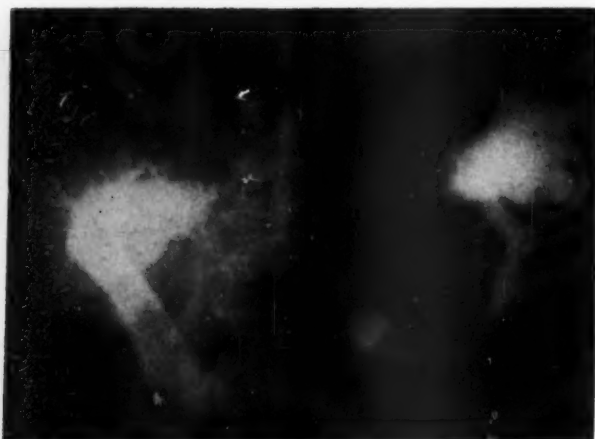


FIG. 4. Case I. Portal cirrhosis and several haematemeses. Intrahepatic vascular pattern shows distortion with loss of gradual fine branching and reduction in calibre of vessels. No gastro-oesophageal collaterals seen. Barium meal subsequently showed duodenal ulceration. In this and subsequent figures: SP = splenic pulp, SV = splenic vein, SM = superior mesenteric vein, PV = portal vein, IVC = inferior vena cava.

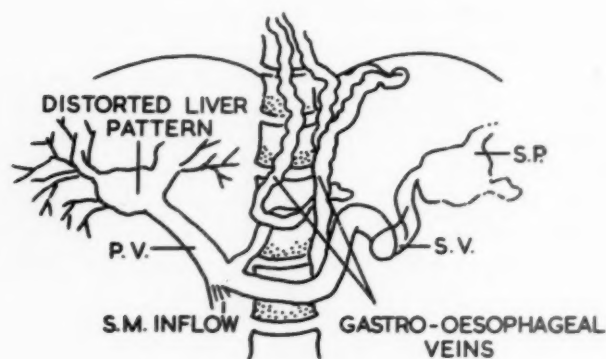


FIG. 5. Case II. Portal cirrhosis. Preoperative venogram showing massive gastric and oesophageal collaterals, a distorted intrahepatic pattern and a portal vein suitable for portacaval anastomosis.

biopsy. Barium meal showed an active duodenal ulcer but oesophageal varices were not seen. The splenic venogram failed to reveal a gastro-oesophageal collateral circulation. (Fig. 4.) In spite of the presence of cirrhosis the patient's bleeding was almost certainly arising from the peptic ulcer and she responded to treatment for this condition.

Clinical management: The surgical treatment of bleeding oesophageal varices depends mainly on the state of the portal vein. If the portal vein is patent, portacaval anastomosis is the operation of choice [42]; but if it is thrombosed, other techniques such as direct ligation of the varices, transection of the oesophagus or lienorenal anastomosis may be considered. The presence of cirrhosis is not an assurance that portacaval anastomosis is possible since portal vein throm-

bosis complicates cirrhosis in approximately 11 per cent of patients [20].

Splenic venography makes it possible to ascertain the state of the portal vein preoperatively; the appropriate surgical procedure can then be selected, and time is not wasted in determining the suitability of the portal vein for anastomosis.

CASE II. During 1955 an 18 year old girl had two severe haematemeses. The spleen was enlarged and a barium meal showed oesophageal varices. The diagnosis was cirrhosis, probably following hepatitis four years previously. Her general condition was good, the haemorrhage did not precipitate drowsiness, stupor or tremor and she had never had ascites. There were no clinical or electroencephalographic changes after one week on a diet containing 120 gm. protein with 10 gm. methionine daily. The splenic venogram

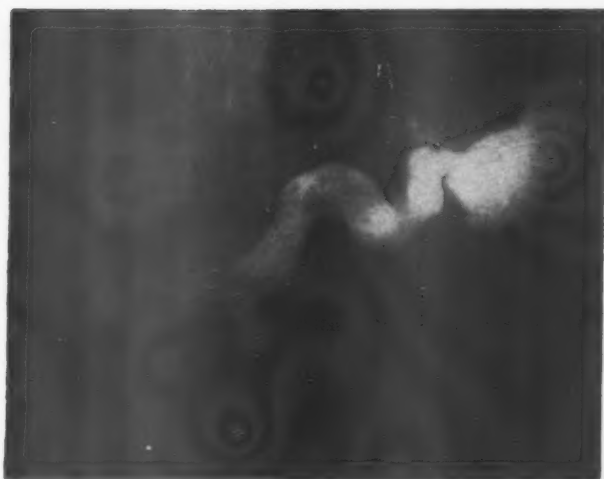


FIG. 6. Case II. Postoperative venogram showing successful portacaval anastomosis. All diiodone flows rapidly into the inferior vena cava and no collateral vessels are seen. The large caval blood flow dilutes the contrast material and renders its visualisation difficult.

showed an extensive oesophageal collateral circulation and a patent portal vein with no evidence of thrombosis. (Fig. 5.) End-to-side portacaval anastomosis was carried out uneventfully and three months later she was well with no further haematemesis. A second venogram demonstrated vena caval filling from the portal vein and complete disappearance of the oesophageal collaterals. (Fig. 6.)

CASE III. A four year old child had three large haematemeses. The spleen was palpable and the skin of the right upper quadrant of the abdomen showed a small scar which had followed a neonatal subphrenic abscess. Barium swallow failed to show oesophageal varices. Portal hypertension following neonatal septic portal vein thrombosis was diagnosed. This was confirmed by splenic venography which showed a mass of collaterals arising from the spleen with only partial filling of a short length of the portal vein. Haematemesis recurred eleven months later. In view of the venographic findings portacaval anastomosis was impossible and an oesophageal transection was performed. In the succeeding nine months haemorrhage has not recurred.

Venography may occasionally be useful as an emergency procedure while bleeding continues.

CASE IV. A forty-five year old housewife was admitted with severe gastrointestinal haemorrhage. She was known to have oesophageal varices but the cause was uncertain. There were no clinical stigmata of cirrhosis and the routine liver function tests were normal. A Sengstaken-Blakemore tube was passed but the bleeding was not controlled. An emergency venogram demonstrated an extrahepatic occlusion of the portal vein which was therefore unsuitable for portacaval anastomosis and a partial oesophago-gastrectomy was performed.

DECEMBER, 1957

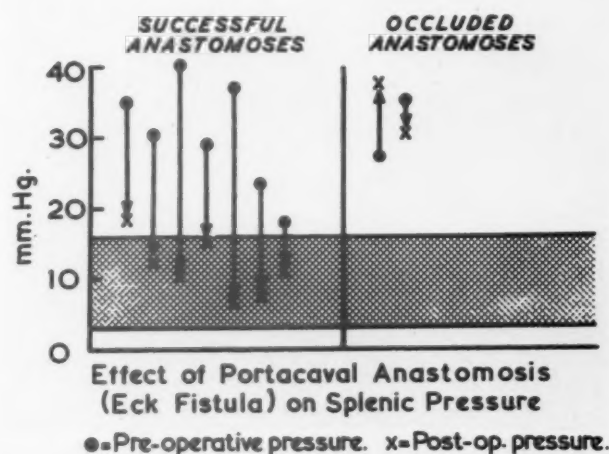
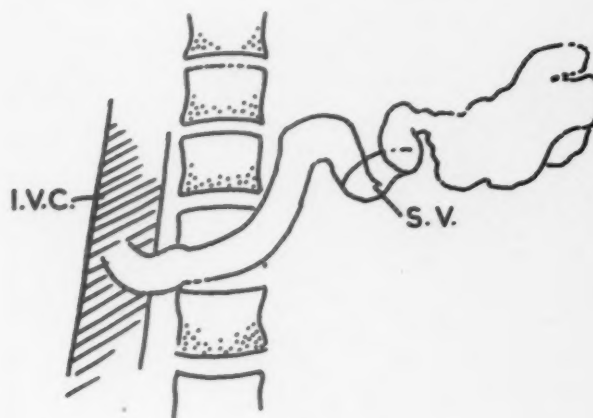


FIG. 7. Successful portacaval anastomosis is followed by fall in intrasplenic pressure. Hatched area represents normal range of intrasplenic pressure. "Successful anastomoses" shown to be patent by venography and "occluded anastomoses" shown to be blocked.

Postoperative investigation of portacaval anastomoses: The mere construction of a portacaval anastomosis is no guarantee of its effectiveness. A satisfactory shunt carries portal blood at a normal pressure, thus allowing the other portal systemic channels to collapse.

Measurement of the splenic pressure and splenic venography provide useful information as to the adequacy of a surgical shunt and the likelihood of future haemorrhage. With a satisfactory shunt the diiodone passes directly from the portal vein into the vena cava and no collaterals are seen. (Fig. 6.)

The occurrence of gastrointestinal haemorrhage after a shunt operation is strongly suggestive of an inadequate anastomosis, and the pres-

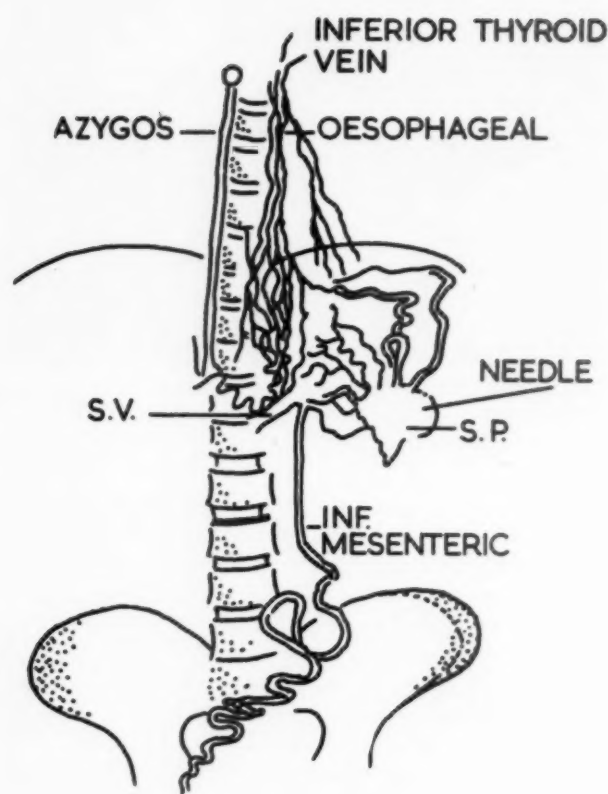


FIG. 8. Case v. Two-year old boy with splenomegaly. Venogram showing extrahepatic portal vein occlusion, the injected diodone reaching the systemic circulation by numerous routes.

ence of a raised intrasplenic pressure confirms this. (Fig. 7.)

Venograms in three patients with haematemesis after occlusion of a portacaval anastomosis showed that a more extensive collateral circulation was present than before the operation. In one of these patients the splenic vein was very large and a subsequent lienorenal anastomosis was performed. In another, although the venogram three months postoperatively showed an occluded shunt with a very extensive collateral circulation, one year later a venogram demonstrated partial recanalisation of the anastomosis with a slight reduction in the size of the other collaterals [8].

Investigation of Splenomegaly. Splenomegaly may be due to well compensated cirrhosis, or extrahepatic portal vein obstruction, occurring separately or together. Especially in children, these conditions may be present without clinical

or biochemical evidence of liver disease and without symptomatic gastrointestinal haemorrhage. In such patients the term "Banti's syndrome" is often used as a diagnostic label. Splenic venography and aspiration biopsy of the liver will usually reveal the cirrhosis or portal vein lesion and exact diagnosis is possible.

CASE V. A two year old boy, while in the hospital for bronchitis, was found to have gross splenomegaly and barium swallow showed oesophageal varices. There had been no previous umbilical or abdominal sepsis and there was no clinical or biochemical evidence of hepatic cirrhosis. Splenic venography revealed an extrahepatic portal vein block (Fig. 8), while aspiration biopsy sections of the liver were histologically normal. The diagnosis was extrahepatic portal vein occlusion, probably congenital.

CASE VI. An eight year old schoolgirl was discovered to have splenomegaly during a routine school

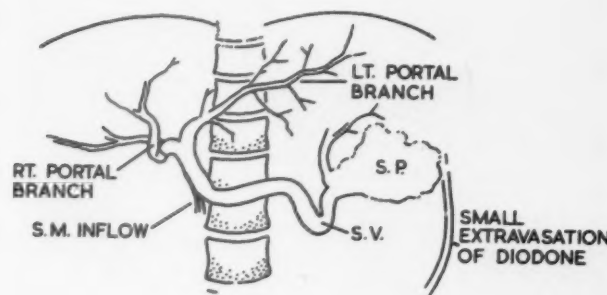
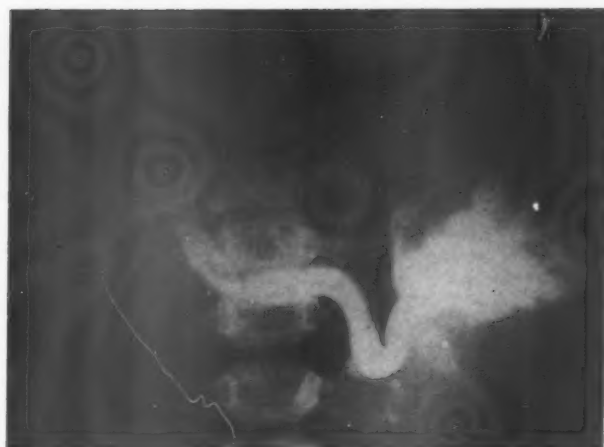


FIG. 9. Case VII. Six year old boy with Gaucher's disease. Venogram shows normal appearances with no collaterals and an even regular branching and reduction in size of the intrahepatic veins. Some diodone has spread beneath the capsule of a considerably enlarged spleen.

medical examination. She gave no history of jaundice or gastrointestinal haemorrhage and was in good general health. The spleen was enlarged to the umbilicus. The liver was not enlarged but a firm edge was palpable in the epigastrium. Routine blood investigations were normal apart from an alkaline phosphatase of 31 King-Armstrong units, a platelet count of 100,000/cu. mm. and a thymol turbidity of 6 units. The urine contained no bilirubin or urobilinogen. No varices were seen on barium examination.

Splenic venography showed patent splenic and portal veins with some oesophageal collateral vessels. Biopsy of the liver revealed a portal cirrhosis. Splenomegaly was associated with portal hypertension due to a well compensated hepatic cirrhosis.

CASE VII. A six year old boy, when admitted to the hospital with a back injury, was discovered to have splenomegaly. He gave no history of abdominal sepsis, jaundice or bleeding apart from frequent epistaxes. On examination he appeared healthy, although slightly undersized. The spleen was enlarged to the umbilicus and the liver was clinically normal. There were no stigmata of cirrhosis or of Gaucher's disease. Investigations were normal except for a weekly positive Hess test and slight thrombocytopenia. Bone marrow examination was normal. Splenic venography showed a normal portal vascular system (Fig. 9), and the intrasplenic pressure was 12 mm. Hg. Extrahepatic portal vein obstruction was thus excluded as the cause of the splenomegaly. Biopsy of the liver, however, revealed the presence of numerous Gaucher cells.

Neuropsychiatric Changes in Patients with Liver Disease. The administration of large amounts of meat to a dog with an Eck fistula will produce ataxia and stupor [21-23] and a similar condition may develop in patients following portacaval

anastomosis [24]. The cerebral intoxication is presumably produced by nitrogenous substances entering the systemic blood stream through the shunt without being detoxicated in the liver. The syndrome is also seen in some patients with large spontaneous shunts [25] and has been termed "portal-systemic encephalopathy" [26]. Portal venography is essential to demonstrate these natural shunts and thus to make a firm diagnosis of chronic portal-systemic encephalopathy. The association of cirrhosis and neuropsychiatric disturbance is not diagnostic of portal-systemic encephalopathy and venography is of particular value in helping to distinguish this from other forms of chronic mental disturbance occurring with cirrhosis.

CASE VIII. At the age of thirty-five a housewife had oedema of both ankles and was found to be anaemic with an enlarged spleen. The following year the patient had an episode of confusion and disorientation which was followed by stupor for five days. After recovery she was treated with a high protein diet and methionine, and for the next three years suffered many times from similar episodes. When seen at the age of forty-one she showed fetor hepaticus, spider naevi and palmar erythema, and the spleen and liver were palpably enlarged. Biopsy of the liver confirmed cirrhosis. The intrasplenic pressure was normal (10 mm. Hg), a finding compatible with the presence of a large portal-systemic shunt, and on splenic venography the whole of the injected diodone passed straight from the splenic vein into the renal vein and then to the inferior vena cava. (Fig. 10.) An increase of dietary protein to 120 gm./day markedly aggravated her confusion and tremor. The presence of a large shunt and the sensitivity to dietary protein clinched the diagnosis of portal-systemic encephalop-

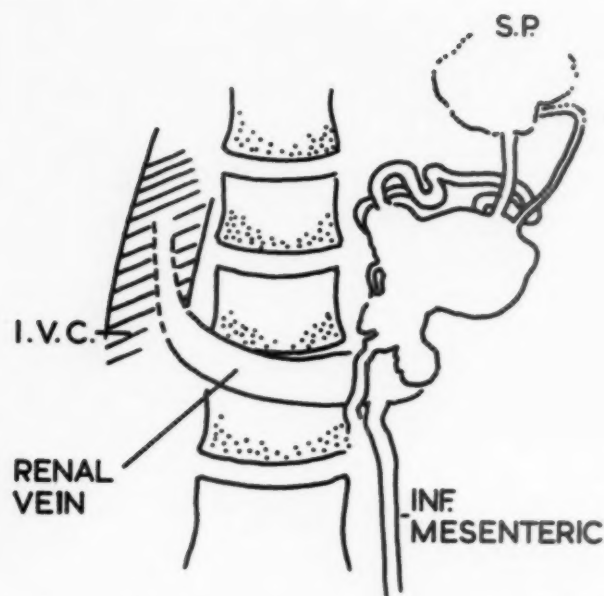


FIG. 10. Case VIII. Portal cirrhosis with intermittent stupor. Splenogram shows an enormous portal-systemic shunt from splenic vein to renal vein and inferior vena cava.

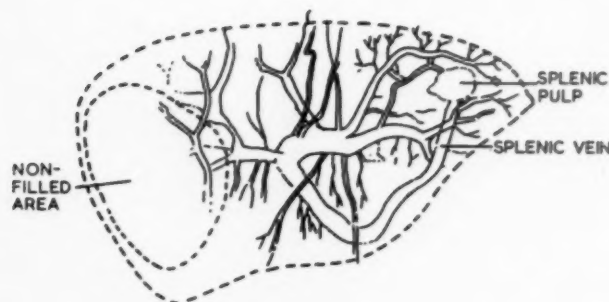


FIG. 11. Case X. Benign hepatic haemangioma. The tumour was situated in the right lobe of the liver and produced a splaying of the intrahepatic vessels with a filling defect in the vascular pattern. The tumour did not apparently derive any blood supply from the portal vein.

athy, and with reduction of the daily protein to 50 gm., the symptoms disappeared.

CASE IX. A man twenty-four years of age, was referred from a mental hospital with the tentative diagnosis of portal-systemic encephalopathy. He had begun to drink spirits at the age of fourteen, having received his social education from his grandfather. At the age of nineteen he spent six weeks in the hospital with hepatitis. He immediately recommenced drinking an average of one bottle of rum daily. Some six months later spider naevi appeared on the patient's arms and occasional tremor of the hands, hypnagogic

hallucinations of little men, fugues and episodes of stupor developed. There was marked palmar erythema, fetor hepaticus and hepatosplenomegaly, and liver biopsy confirmed hepatic cirrhosis. Splenic venography demonstrated a patent portal vein with no evidence of a collateral circulation. A diet of 120 gm. protein with 10 gm. added methionine daily for ten days produced no worsening of the mental or neurologic condition. It was concluded that he was a hysterical psychopath.

The Investigation of Suspected Hepatic Tumours. Primary or secondary neoplasms of the liver may

TABLE II
EXTRAHEPATIC PORTAL VEIN OBSTRUCTION AND ASCITES

Case No. Sex	Age (yr.)	Associated Disease	Duration of Ascites (mo.)	Serum Albumin (gm./100 ml.)	Serum Globulin (gm./100 ml.)	Ascitic Fluid Protein (gm./100 ml.)	Intrasplenic Pressure (mm. Hg)
xi, M	63	Active pulmonary tuberculosis	14	2.5	4.8	4	25
xii, F	29	Inactive pulmonary sarcoidosis	2	3.3	3.3	...	27
xiii, F	79	None found	8	3.3	3.3	1.2	12

produce sufficient distortion of the portal vein and its branches to be seen on the venogram [27,28]. The usual finding is of a filling defect in the intrahepatic vascular pattern.

CASE x. A thirty-five year old Cypriot woman complained of vague pain in the right upper quadrant of the abdomen and was found to have a firm liver palpable below the costal margin. Routine tests were normal. Splenic venography showed a generally enlarged liver with a filling defect in the right lobe. (Fig. 11.) Biopsy of the liver in the area of the filling defect revealed the presence of a benign cavernous haemangioma. No complications resulted from the venogram or liver biopsy. The general enlargement of the liver was possibly associated with the presence of further smaller haemangiomas, as these tumours are commonly multiple.

The Investigation of Ascites of Obscure Origin. Most attempts to produce ascites experimentally solely by obstruction of the portal vein have failed [29-34]. Because of this, and the difficulty of estimating the portal venous pressure in man, the role of portal hypertension in the production of ascites is obscure. Baggenstoss and Wollaeger [35], surveying the postmortem records of the Mayo Clinic, could find only fifteen cases of isolated chronic obstruction of the portal vein; five of these had ascites.

Splenic venograms and pressure measurements were obtained in three patients with ascites of uncertain aetiology. All three had extrahepatic portal vein occlusion and showed no other cause for the ascites. Aspiration biopsies of the liver revealed no evidence of portal cirrhosis and the cause of the portal occlusion was obscure. In Case xi the patient with active pulmonary tuberculosis had had previous leg-vein thrombosis; the patient in case xii apparently had inactive pulmonary sarcoidosis; in case xiii

the patient had no detectable associated disease (Table II.)

CASE xi. A sixty-three year old man with active pulmonary tuberculosis had ascites for eighteen months. Many paracenteses had been performed, a total of 260 pints of fluid having been removed. Numerous collateral veins were visible on the anterior abdominal wall. After paracentesis these persisted, but the liver and spleen were not palpable. Serum bilirubin, alkaline phosphatase, thymol turbidity, zinc sulphate turbidity, cholesterol, and bromsulphalein retention were normal. The serum albumin was 2.5 gm. per cent and the globulin 4.8 gm. per cent. A barium meal showed oesophageal varices. Aspiration biopsy of the liver produced a large specimen which was histologically normal apart from the presence of one small granuloma, possibly an early tubercle. No tubercle bacilli were found in the ascitic fluid by direct examination or after culture and inoculation of a guinea pig. The intrasplenic pressure was raised (25 mm. Hg) and venography revealed an extrahepatic portal vein obstruction with some paraportal channels. The hepatic vein was shown to be patent by catheterisation and the wedged-pressure normal (8 mm. Hg) [36,37]. These observations confirmed the presence of extrahepatic portal obstruction [9], and at the time of catheterisation the inferior vena cava was shown to be patent as far as the iliac veins.

Cardiac, renal or peritoneal disease and hepatic cirrhosis were excluded. The ascites was associated with a low serum albumin level, possibly secondary to repeated paracentesis or resulting from pulmonary tuberculosis.

The serum albumin level was much reduced in only the first of these three patients. The rather low figure in Case xii might be explained by a haematemesis occurring just before the development of ascites [35] but in Case xiii no cause for a low serum albumin was found apart from repeated paracenteses which did not, of course, precede the ascites.

INTRASPLENIC PRESSURE AND ITS RELATION TO THE PORTAL COLLATERAL CIRCULATION AND GASTROINTESTINAL HAEMORRHAGE

The venographic demonstration of large splenic and portal veins, or of a portal collateral circulation, is not definite evidence of portal

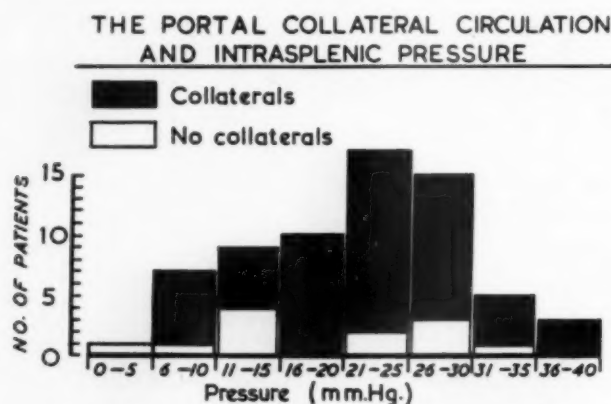


FIG. 12. The relation between the intrasplenic pressure and the presence or absence of collaterals in sixty-six patients with portal or biliary cirrhosis. In general collaterals are associated with an increased intrasplenic pressure but some patients with large collaterals have a normal pressure and some patients with a high pressure show no collaterals. No strict correlation could be demonstrated between collaterals and portal hypertension ($0.1 < p < 0.2$).

hypertension. Large splenic veins were seen in three patients with Gaucher's disease, none of whom had a raised intrasplenic pressure. Portal collaterals are usually associated with portal hypertension but if they are very large the portal pressure may be normal. Similarly, the absence of collaterals does not exclude the presence of portal hypertension and no direct correlation was found between the level of portal pressure and the mere presence or absence of a portal collateral circulation in sixty-six patients with portal or biliary cirrhosis. (Fig. 12.) Previously, on the basis of a smaller series of patients it had been concluded that the presence of collaterals did correlate with the presence of portal hypertension [6].

A raised portal pressure may fall naturally; in one patient with portal cirrhosis the intrasplenic pressure fell spontaneously from 25 to 12 mm. Hg in twelve months. A venogram at the time of the second, normal, splenic pressure measurement showed enormous oesophageal vessels which had presumably lowered the portal pressure.

The relation between the intrasplenic pressure and the occurrence of gastrointestinal haemor-

rhage was studied in two groups of patients with oesophageal varices associated with portal cirrhosis or extrahepatic portal vein obstruction. (Fig. 13.) The intrasplenic pressure was significantly higher in the group who had suffered previous haemorrhage, although bleeding had

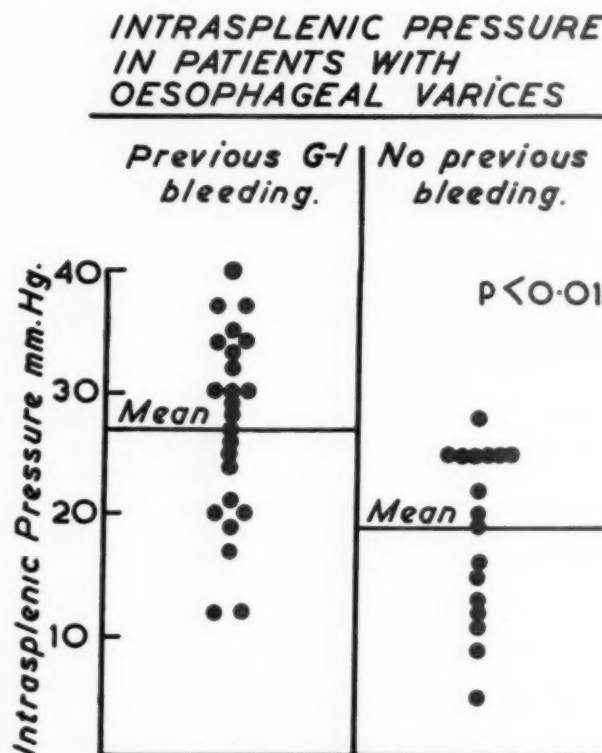


FIG. 13. The intrasplenic pressure in patients with oesophageal varices with and without previous gastrointestinal haemorrhage. The pressure is significantly higher ($p < 0.01$) in the group with previous haemorrhage, but several patients in this group have pressures in the normal range.

recently occurred in three patients with varices and a normal pressure. In these patients the low pressure was associated with an extremely large oesophageal circulation.

PORTAL VEIN OCCLUSION

In six patients with portal cirrhosis no diodone entered the portal vein after intrasplenic injection. In every instance there was an extremely large portal-systemic collateral circulation. In three all the injected diodone entered the inferior mesenteric vein, in two it passed through a mass of tortuous vessels from the splenic vein into the renal vein and then to the inferior vena cava, and in one patient the diodone passed entirely into a massive circulation around the oesophagus. All six patients suffered from portal-

systemic encephalopathy and in five this was the presenting feature of their illness. The diagnosis of portal vein occlusion was confirmed in two of these patients by the finding of high intra-splenic pressures (25 and 20 mm. Hg) with low occluded hepatic vein pressures (12 and 7 mm. Hg) [10]. These two patients and one other were autopsied twenty-four, twelve and two months, respectively, after venography. In the first two patients the portal vein showed evidence of an old thrombosis which had partially recanalised and in one patient the thrombus was localised to the main bifurcation of the portal vein, the trunk of which was patent. In the third patient the portal vein was completely occluded by very fresh thrombus, suggesting that the vein was not in fact thrombosed at the time of the venogram one month before. The diagnosis of portal vein occlusion was not confirmed by autopsy in the other three patients who are still alive.

Portal vein obstruction in the absence of cirrhosis was seen in twelve patients. In ten patients the liver was histologically normal and in two, with pulmonary tuberculosis and sarcoidosis, a few hepatic granulomas were seen. In one patient the portal vein was obstructed at the porta hepatis where it entered a fibrous mass, the result of a previous liver abscess.

COMMENTS

Splenic venography is a simple technic, and in this series of 126 investigations there were few complications provided that patients with a bleeding tendency were excluded. It has been suggested that the procedure should be performed only in the operating theatre immediately prior to surgery, but the advantage of a careful preoperative study of the venogram is considerable. Moreover, although haemorrhage is rare it may be delayed and in one patient occurred five days after venography. The absence of overt bleeding at laparotomy is thus no guarantee that it will not occur in the post-operative period.

Venography is of particular value in determining the state of the portal vein in patients under consideration for portacaval anastomosis. It is therefore important to know the significance of non-filling of the portal vein on venography. This may undoubtedly result from the use of inadequate amounts of diodone and from taking insufficient films [8]. In this series 40 ml. of 70 per cent diodone has been found to be sufficient

for an adult and at least five films have been taken in every case. If the venogram is technically satisfactory, non-filling of the portal vein does, in most instances, indicate its occlusion. However, in rare cases, when the collateral circulation is especially large, and particularly when it takes one route such as the inferior mesenteric vein or large oesophageal veins, it is possible that the diodone may be carried into this channel by the main stream of superior mesenteric blood, so that a patent portal vein is not filled.

Leger [38] described four patients in whom the portal vein did not fill on venography. In one patient this was due to extravasation of diodone and inadequate filling of the portal system; in the other three patients the injected material was carried into large gastric and oesophageal collaterals, and postmortem examinations revealed that two patients had patent portal veins and the other a localised thrombus at the bifurcation of the portal vein. Two patients in this series confirm Leger's findings. While, therefore, a false appearance of portal vein thrombosis may be obtained if the collateral circulation is very large, this does not invalidate the venographic diagnosis of portal vein occlusion in the absence of such massive collaterals. Moreover, in the six patients with cirrhosis in this series in whom no portal vein filling was seen, and in whom such a large portal-systemic circulation was observed, the main disability was portal-systemic encephalopathy and portacaval anastomosis was not under consideration.

The present series confirms the previous experience that venography is superior to a barium meal examination in demonstrating an oesophageal collateral circulation [6,8]. Barium swallow shows only the submucosal vessels whereas venography may demonstrate paraoesophageal veins as well.

Venography has also proved of great value in the diagnosis of the cause of splenomegaly due to extrahepatic portal or splenic vein occlusion. This condition may be present for some years without evidence of gastrointestinal haemorrhage, and in some instances, when most of the portal blood is diverted into a large azygos or inferior mesenteric vein, apparently even without oesophageal varices.

The technic has facilitated the understanding of the syndrome of chronic portal-systemic encephalopathy by showing that large portal-systemic shunts may develop naturally in patients who have not undergone a surgical opera-

tion, and is now of value in the distinction of this from other causes of mental disorder in patients with cirrhosis.

The part played by portal hypertension in the production of ascites is obscure but the occasional finding of ascites caused apparently by extrahepatic portal vein obstruction alone, together with the reported disappearance of fluid after portacaval anastomosis [39], suggests that it is of some importance. Splenic venography has so far provided the only antemortem diagnosis of the presence of extrahepatic portal vein obstruction in three patients with ascites of unexplained aetiology, but it is of interest that the intrasplenic pressure was high in only two.

Measurement of the intrasplenic pressure may be used to establish the presence of suspected portal hypertension and to follow its clinical course. In combination with hepatic vein catheterisation the technic is useful in the confirmation of portal vein occlusion [10].

Comparison of the results of splenic venography and intrasplenic pressure measurement has shown that portal hypertension may be present in some patients without a portal-systemic collateral circulation and that if large shunts are developed either naturally or by operation the hypertension may be relieved. Measurement of the splenic pressure is one of the simplest methods of determining the state of a portacaval shunt postoperatively [40].

In general, the intrasplenic pressure is higher in patients with oesophageal varices which have bled than in patients with varices which have never ruptured; but in a few instances, where the oesophageal collaterals have been very large, bleeding has occurred with a normal intrasplenic pressure [37]. This suggests that other factors such as ulceration [43] or reflux may be important in the production of haemorrhage from varices and that, to be effective, surgical anastomoses must not only reduce the pressure in the oesophageal vessels but be of sufficient size to carry the entire portal blood at a normal pressure and thus allow the oesophageal varices to collapse.

SUMMARY

The technics of intrasplenic pressure measurement and splenic venography are briefly described. One hundred and twenty-six venograms were performed with few serious complications. The main indications for the procedure were: gastrointestinal haemorrhage; neuropsychiatric

disturbances in patients with cirrhosis; splenomegaly, hepatomegaly and ascites of uncertain etiology; and suspected hepatic tumours.

Comparison of intrasplenic pressure with venographic appearance shows that portal hypertension may be present in the absence of a portal-systemic collateral circulation and that the development of large natural or artificial portal-systemic shunts may be followed by a fall in the intrasplenic pressure.

Non-filling of the portal vein may be due to portal vein occlusion, the presence of a large collateral circulation with deviation of the injected material, or to an unsatisfactory technic. The significance of this finding and the interpretation of the venogram are discussed.

Most patients who have suffered haemorrhage from oesophageal varices have portal hypertension, but a few with large varices have a normal portal pressure, suggesting that other factors may be important in the production of haemorrhage and that shunts should be large enough to carry the entire portal blood and allow collapse of these vessels.

Acknowledgment: We wish to thank Mr. C. R. Brecknell and Mr. F. Saunders for the photographs and diagrams and also Messrs. Smith, Kline and French International Company, Philadelphia, for their support.

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Effect of L-Arginine on Elevated Blood Ammonia Levels in Man*

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ELEVATED blood ammonia levels and toxicity in man have been observed to result from amino acid administration [1,2]. L-Arginine has been shown to protect against this blood ammonia rise and associated toxicity [1]. Similar observations were made during intravenous amino acid administration in dogs [3-6] and intraperitoneal injection in rats [7-9]. The protective action of L-arginine apparently is the result of its activity in the hepatic Krebs-Henseleit cycle through which ammonia is converted to urea [3,6,9].

The present studies were undertaken to assess the effect of L-arginine on the clinical status and blood ammonia concentration of patients with elevated blood ammonia levels caused by exogenous ammonia. Two groups were studied: one group with severe hepatocellular disease, elevated blood ammonia levels and hepatic encephalopathy; the other consisted of subjects with normal hepatic function in whom blood ammonia elevation was induced by administration of ammonium salts directly into the systemic circulation.

METHODS AND MATERIALS

Arterial and venous blood ammonia levels were measured in a group of patients with severe, advanced liver disease, generally in hepatic failure, and also in normal subjects and a group of patients without evidence of liver disease who had been admitted to the Clinical Center of the National Institutes of Health. Ammonia determinations were performed by a previously described modification of the Seligson technic [7] on samples of blood obtained practically simultaneously from the brachial artery and antecubital vein or, occasionally, from the femoral artery and vein.

The L-arginine HCl used in these studies was free of other amino acids on paper chromatographic analy-

sis.‡ L-Arginine HCl solutions (0.5 M) were prepared in pyrogen-free water and sterilized in the autoclave at 120°C. at a pressure of 20 pounds per square inch for fifteen minutes. Each lot of L-arginine was tested and found to be active in man in reducing the blood ammonia rise associated with intravenous glycine administration to fasted subjects. Diammonium citrate solutions (0.5 M) were prepared with pyrogen-free water and sterilized in the autoclave as described. All solutions were tested by the Biologics Standards Division of the National Institutes of Health and found to be free of pyrogen and bacterial contamination.

L-Arginine Administration. Seven patients with advanced liver disease and hepatic encephalopathy due to neoplastic replacement of the liver or acute hepatitis, and generally without evidence of portal-systemic collateral circulation, and one patient with cirrhosis and a well developed portal-systemic collateral circulation received L-arginine in an effort to alleviate the hepatic encephalopathy and reduce the blood ammonia level. L-Arginine was administered intravenously over sixty to 120 minute periods utilizing a constant infusion pump. Serial blood samples were obtained for ammonia analysis from the brachial artery and, when feasible, also from an antecubital vein prior to, during, and for at least two hours after the infusion of arginine. Blood ammonia measurements were made at intervals of twenty to thirty minutes. Because the effect of L-arginine when injected during administration of ammonia-inducing amino acids is evident within fifteen minutes [7], it was considered that if L-arginine was going to alter the blood ammonia level, a change should be evident during or shortly after arginine administration. Neurologic examinations were conducted by the same observer before, and two to three hours and twenty-four hours after the infusions. Mental function was

‡ L-Arginine HCl was made available by Dr. Jesse P. Greenstein of the Laboratory of Biochemistry, National Cancer Institute, and was also obtained from the Mann Research Laboratories, Inc., New York 6, N. Y. Ammonium chloride solutions (0.4 M) were obtained from the Baxter Laboratories, Morton Grove, Illinois.

* From the Metabolism Service, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare.

† Present address: New York, N. Y.

evaluated at more frequent intervals. Classification of the stages of encephalopathy was based on the criteria of McDermott and Adams [10]. Normal mental function was recorded as zero. Drowsiness, slowness of response or incoherence of thought was rated as one. Severe mental confusion with disorientation for time or place, and incontinence of sphincters was recorded as two. Stupor, a significant reduction in spontaneous activity with mental dullness, was graded three. Coma, a complete lack of awareness of any externally applied stimulus, was graded as four.

A small amount of L-arginine HCl (5 mM) was given initially because this amount had been effective in reducing the blood ammonia rise when an L-amino acid mixture or glycine was infused into fasting subjects [7] and because the potential toxicity of intravenous L-arginine HCl in patients with liver disease was unknown. Subsequently the dose was progressively raised to 140 to 185 mM (29.5 to 39 gm.) without apparent toxicity.

Elevated blood ammonia levels were produced in five subjects without liver disease by intravenous infusion of ammonium citrate or ammonium chloride solutions. Ammonium administration was selected as a reproducible, controlled example of blood ammonia elevation of the non-hepatic exogenous type. Most of these subjects had neoplasms of the head and neck region, esophagus or stomach without distant metastases and required maintenance of nutrition by means of a tube passing to the stomach through a cervical esophagostomy. There was no evidence of hepatic disease by history or on physical and laboratory examination in these five subjects. Normal blood ammonia levels were characteristic of this group. A sixth subject (W. M.) with hepatoma and abnormal liver function tests but no evidence of hepatic failure also received ammonium citrate intravenously. In the eighteen hours preceding each study the subject received no protein in his diet.

Preliminary observations demonstrated that infusion of 0.015 mM ammonia/kg./minute would produce the desired blood ammonia elevation. Side effects such as nausea and retching observed at higher rates of administration were minimal. Constant blood ammonia concentrations were maintained throughout two to four hours of ammonium administration.

L-Arginine HCl was administered intravenously for sixty or one hundred minute periods concomitantly with ammonium administration and at rates equal to or twice that of the ammonium ion (in terms of mM per minute). All infusions were administered with a constant infusion pump into a vein in an otherwise free upper extremity. When two solutions were infused simultaneously, each solution was administered by a separate pump and, generally, into a second vein. Serial blood ammonia determinations were performed on antecubital venous blood samples removed through a Cournand needle in the opposite arm. In many studies simultaneous arterial blood samples were obtained from the brachial artery.

RESULTS

Arterial and Venous Blood Ammonia Levels.

Elevated arterial blood ammonia concentrations were usually observed in patients with severe hepatic disease. (Fig. 1.) When simultaneous arterial and venous blood ammonia determinations (eighteen observations) in subjects with hepatic failure are compared with forty-six similar observations in subjects without liver disease, it is evident that the presence of severe hepatic disease correlates better with arterial blood ammonia concentration than with the venous blood level. (Fig. 1.)

A further contrast between the normal and hepatic failure groups is seen when the difference between arterial and venous blood ammonia levels is measured. (Fig. 2.) Almost all of the subjects without liver impairment showed a negative A-V difference, indicating the release of a slight amount of ammonia from the peripheral tissues. On the other hand, patients with severe liver disease usually had positive A-V differences indicating peripheral removal of ammonia. In general the A-V difference correlated well with arterial blood ammonia concentration; the higher the ammonia level, the greater the A-V difference. Furthermore, a few patients with liver impairment whose arterial blood ammonia level was within the normal range had positive (abnormal) A-V differences.

L-Arginine Administration in Hepatic Failure.

Eight patients with severe disease of the liver and signs of hepatic encephalopathy were given 5 to 185 mM of L-arginine HCl over sixty to 120 minutes. The diagnosis, liver function tests, stage of encephalopathy, initial blood ammonia levels and response to L-arginine are assembled in Table 1. L-Arginine produced no change in the clinical status of any of the patients, and only V. M. (Case 1) had a significant fall in blood ammonia concentration during arginine infusion. Although factors other than hepatic failure may have contributed to neurologic signs, postmortem examination of the brain was performed in six of these patients and revealed evidence of metastatic neoplasm to the brain only in patient V. M. The fall in blood ammonia noted in Case 1 during arginine administration was not substantiated in seven other patients in spite of substantial increase in arginine dosage. It is possible that the blood ammonia change in this patient was entirely unrelated to arginine administration, since spontaneous fluctuations in the blood ammonia level of this magnitude

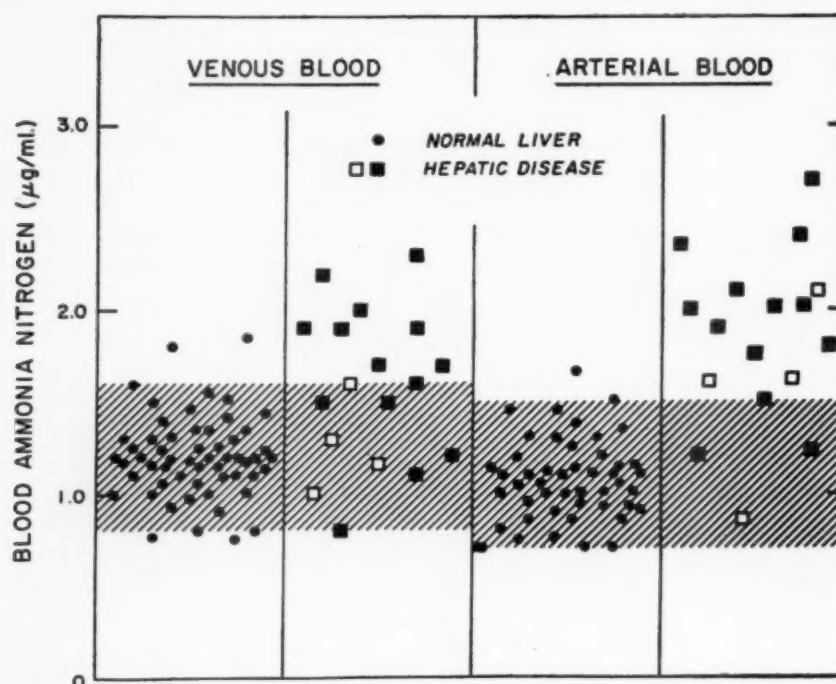


FIG. 1. Blood ammonia concentrations in subjects with and without liver disease. (● Normal liver, □ liver disease without encephalopathy, ■ liver disease with encephalopathy.) The range of normal (± 2 Standard Deviation) is indicated by the shaded areas.

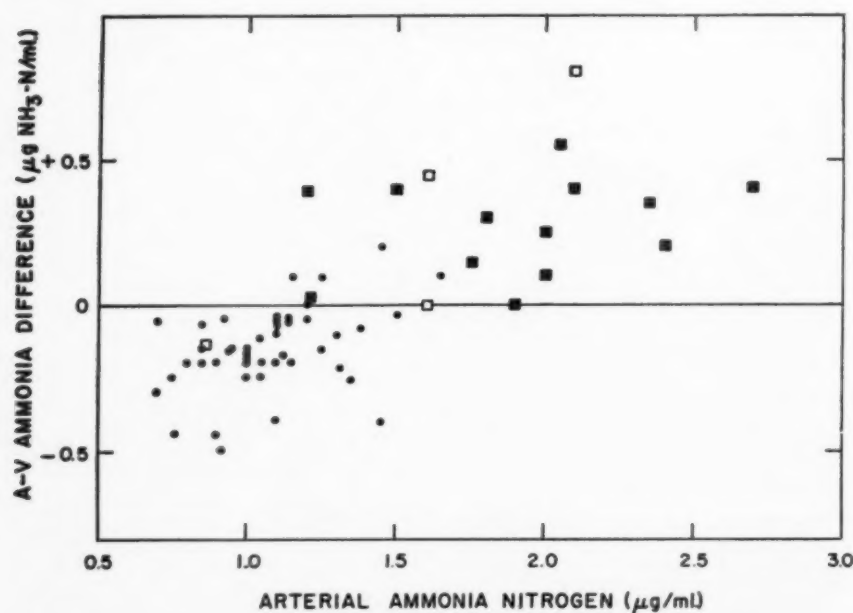


FIG. 2. Relationship of peripheral A-V difference to the arterial blood ammonia concentration. (● No liver disease, □ liver disease.)

have been observed in other patients with hepatic encephalopathy.

L-Arginine Administration in Subjects Receiving Ammonium Salts. Intravenous administration of ammonium salts to subjects without detectable disease of the liver produced a prompt rise in

the blood ammonia concentration (Fig. 3), the arterial level becoming higher than the venous level. This A-V difference resembles the situation found in patients with advanced liver disease, as already noted. At the rate of ammonium administration employed, the blood ammonia

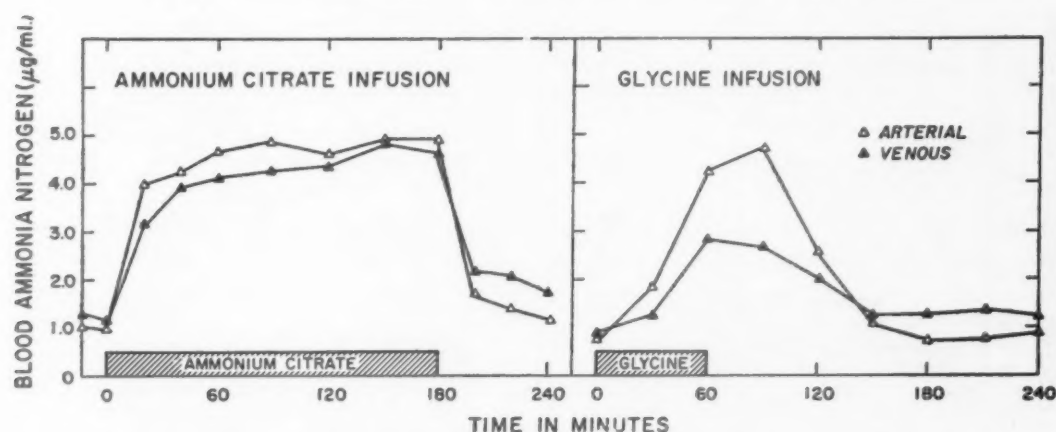


FIG. 3. Arterial and venous blood ammonia changes associated with intravenous infusion of ammonium citrate and of glycine.

reached and maintained a constant level until cessation of the ammonium infusion, when it fell promptly to normal. The arterial blood ammonia returned to a level below that of the peripheral vein.

For testing the effectiveness of L-arginine on the elevated blood ammonia levels induced by exogenous ammonia administration, subjects with normal liver function were selected so that the maximal effect of L-arginine would be ob-

tained without any impairment attributable to poor hepatic function. A rate of ammonium infusion was chosen so that the blood ammonia levels were somewhat higher than those observed in hepatic failure, but were about the same as those produced by intravenous administration of glycine (Fig. 3) or of an arginine-deficient L-amino acid mixture [7]. L-Arginine was given in eight studies in six subjects and failed to lower the blood ammonia appreciably, either when

TABLE I
EFFECT OF L-ARGININE INFUSION DURING HEPATIC FAILURE

Patient	Diagnosis	Encephalopathy Stage	Total Bilirubin (mg. %)	Alkaline Phosphatase (Bodansky units)	Cephalin Flocculation	Thymol Turbidity (units)	Serum Albumin (gm. %)	L-arginine Total Dose (mM.)	Source of Blood	Blood Ammonia Concentration ($\mu\text{g. NH}_3\text{N/ml.}$)								
										Before Arginine	Minutes from Start of L-arginine							
											30	60	90	120	150	180	240	300
V. M.	Carcinoma of breast	III	5	20	3+	6	1.9	5	V	1.9	1.85	1.75	1.6	1.5	...	1.3	1.4	1.6
M. L.	Hepatoma	II	8	7	2+	29	1.3	5	A	2.35	...	2.7	...	2.5	...	2.5	2.7	2.4
B. H.	Acute myelocytic leukemia	III	10	2	3+	2	1.4	20	A V	1.2 0.8	1.0 0.7	1.1 1.0	0.8 0.7	1.1 0.6	0.9 0.8	1.1 0.9	1.2 1.0	1.2 1.0
M. W.	Carcinoma of breast	II	19	24	0	7	1.3	187	A V	1.9 1.9	1.85 1.95	2.05 1.8	1.85 1.75	1.9 1.6	2.1 1.8	2.1 2.05
J. R.	Viral hepatitis	III	26	5	4+	21	1.4	180	A	2.1	...	2.1	...	2.1	2.2	2.1
F. H.	Carcinoma of breast	I	21	38	3+	7	1.5	180	A V	1.75 1.6	1.65 ...	1.9 ...	1.5 ...	1.6 1.5	2.1 ...	2.2 2.2	2.25 2.25	...
M. G.	Carcinoma of breast	II	6	11	2+	17	1.8	145	A	2.0	2.1	2.0	1.9	1.9	1.9	2.1	2.0	...
D. R.	Cirrhosis	II	5	9	1.4	140	A V	2.7 2.3	2.7 2.5	2.75 2.3	2.7 2.85	2.7 2.7	2.5 2.5	2.5 2.3	2.6 2.5	...

NOTE: Duration of L-arginine infusion indicated by double lines.

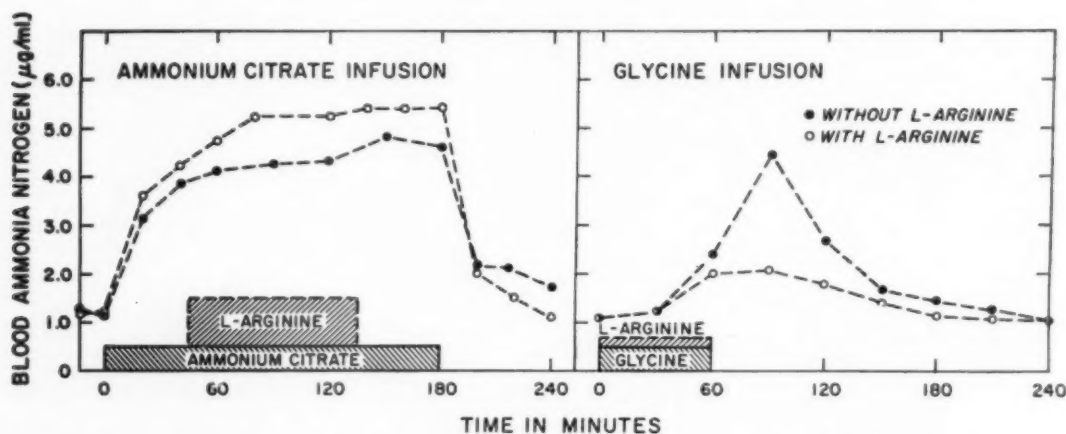


FIG. 4. Comparison of the effect of L-arginine on the blood ammonia elevation due to ammonium citrate infusion and due to glycine infusion. Patient G. S. was the subject for all of the studies. In the ammonium infusion study ammonium citrate was given at the rate of 0.015 mM ammonium/kg./minute; the glycine was administered at a rate of 0.070 mM/kg./minute; the L-arginine at 0.006 mM/kg./minute.

given during the first sixty minutes of an 120-minute ammonium infusion (in equimolar amount to the ammonium ion), or from the forty-fifth to 145th minute of 180 minute ammonium salt infusions even though given at a molar rate twice that of the ammonium ion. (Fig. 4, Table II.) The total dose in these later studies was 3 mM/kg., an amount much greater than that needed to prevent blood ammonia rises in subjects receiving certain amino acids intravenously. (Fig. 4.)

COMMENTS

Clinical situations associated with elevated blood ammonia levels may be considered in two groups on the basis of the primary source of ammonia: hepatic or non-hepatic. The hepatic source is significant when the liver releases ammonia into the circulation. [4] This occurs when certain amino acids, e.g., glycine, are administered parenterally in the presence of a relative arginine deficiency. In the non-hepatic group ammonia may originate endogenously in an organ other than the liver, such as the kidney, or from a source essentially outside the organism (exogenous source) e.g., the gastrointestinal tract or from ammonium salts given intravenously.

The common factor in the non-hepatic group is the entrance of ammonia directly into the general circulation. Clinically this occurs most frequently in cases in which the portal blood, with its high ammonia content of intestinal origin, bypasses the liver via portal-systemic anastomoses, as in cirrhosis or surgical porta-

caval shunts. Such bypassing of the liver cell occurs also when there is severe hepatocellular damage; in this instance ammonia in the portal blood passes through the damaged liver into the general circulation [17]. Likewise during intravenous ammonium chloride therapy for alkalosis, exogenous ammonia is introduced directly into the general circulation [12-14].

In the studies reported here the elevated ammonia levels in patients with non-hepatic (exogenous) ammonia sources were not responsive to L-arginine in a manner that might be expected by direct extrapolation from the animal experiments noted earlier. These present results are also in marked contrast to our observations on the effectiveness of L-arginine against the ammonia elevation resulting from amino acid administration in man [1]. This discrepancy appears to be at least partially explained by differences in the source of ammonia in these two situations.

Recent investigation of the ammonia sources during glycine administration and of the site of L-arginine action has provided considerable insight into the role of L-arginine in reducing blood ammonia levels [4]. These studies revealed that ammonia was released into the blood stream from both the liver and kidney when glycine was infused into fasted dogs. The liver appeared to be the major ammonia source. When L-arginine was administered, ammonia release from the liver stopped, hepatic removal of ammonia from the blood became evident, and the peripheral blood ammonia level fell. There was no change in renal ammonia production. Other

TABLE II
EFFECT OF L-ARGININE ON BLOOD AMMONIA ELEVATION INDUCED BY AMMONIUM INFUSIONS

Subject	Ammonium Infusion			L-arginine		Blood Ammonia Concentration ($\mu\text{g. NH}_3\text{ N/ml.}$)																
	Form	Rate (mM $\text{NH}_4\text{/kg./min.}$)	Duration (min.)	Rate (mM/kg./min.)	Time* (min.)	Sample Source	Before Infusion†		Minutes from Start of Ammonium Infusion													
									20	40	60	90	120	140	160	180	200	220	240			
G. S.	Citrate	0.015	180	A V	1.0 1.3	1.0 1.2	4.0 3.2	4.2 3.9	4.7 4.2	4.9 4.3	4.6 4.4	5.1 5.0	5.0 4.9	5.0 4.7	1.8 2.2	1.4 2.1	1.2 1.5			
	Chloride	0.014	160	A V	1.2 1.05	1.1 1.05	3.3 1.9	3.5 2.1	4.0		
	Citrate	0.015	180	0.030	45-145	A V	1.05 1.15	0.95 1.2	4.4 3.6	4.8 4.2	5.2 4.8	5.8 5.2	5.8 5.3	5.4 5.4	5.6 5.5	5.8 5.5	1.6 2.0	1.2 1.5	1.0 1.1			
	Chloride	0.014	180	0.030	45-145	A V	1.1 1.3	1.0 1.3	4.1 2.8	4.3 3.7	4.8 4.3	6.0 5.1	5.7 5.6	4.8 5.0	4.6 4.3	4.4 4.5	1.5 2.0	1.3 1.5	1.0 1.3			
J. F.	Citrate	0.014 ^a	180	A V	1.1 1.2	4.3 3.5	4.6 4.1	5.2 4.5	5.4 4.9	5.2 4.5	5.0 4.5	4.9 4.5	5.4 4.9			
	Citrate	0.014	180	0.028	50-150	A V	1.2 1.4	1.4 1.5	4.3 2.3	4.9 2.3	5.1 3.0	5.1 2.8	4.2 3.1	4.4 3.3	4.8 3.7	4.8 3.1	2.2 2.3	1.7 1.9	1.5 1.7			
E. Y.	Citrate	0.015	180	A V	1.2 1.2	4.9 3.0	5.2 3.8	5.9 4.0	5.4 4.8	5.8 5.3	5.8 5.4	6.2 5.4	6.2 5.5			
	Citrate	0.013	180	0.030	45-145	A V	0.8 1.0	4.7 3.8	5.2 3.0	5.0 2.8	5.8 3.0	5.8 2.7	5.8 2.6	1.5		
W. P.	Citrate	0.015	120	V	1.35	4.9	5.1	6.0	6.2	2.4	1.7	1.4			
	Citrate	0.015	120	0.015	0-60	V	1.1	5.6	6.3	6.0	2.3	1.4	1.3			
M. M.	Citrate	0.015	120	V	1.3	4.6	5.1	6.1	5.1	2.0	1.4	1.4			
	Citrate	0.015	120	0.015	0-60	V	1.2	4.8	5.3	5.6	5.4	2.3	1.4	1.3			
W. M.	Citrate	0.014	150	0.028	45-105	V	0.8	4.1	4.1	4.8	5.2	5.2	1.4	1.2	1.0			
	Citrate	0.015	180	0.028	45-145	V	0.7	5.2	5.9	5.7	5.7	5.4	5.5	5.4	5.2	1.7	1.8	0.8			

* Time of arginine infusion is presented in terms of the minutes from the start of ammonium infusion. With subject, G. S., the arginine infusion was started forty-five minutes after initiation of the ammonium infusion and ended 100 minutes later, 145 minutes after the ammonium infusion was begun.

† In several studies, two preinfusion blood ammonia measurements were made with at least twenty minute intervals.

studies have demonstrated that a rise in blood ammonia did not develop in recently fed subjects [1,3,4]. These findings suggest that when adequate amounts of L-arginine are present "ammonia" resulting from amino acid metabolism within the liver is converted to urea and is not available for diffusion as ammonia into the blood stream. This contrasts with the arginine-deficient state in which ammonia is released into the blood. Thus a major action of L-arginine is the diversion and removal of the hepatic endogenous source of ammonia prior to release into the blood.

Removal of ammonia that is already circulating in the blood may be a more complex process than the handling of nitrogenous products

formed in the liver during administration of amino acids. Ammonia must be transported from the blood into the liver cell and then pass through the several steps by which ammonia is prepared for entrance into the Krebs urea cycle [15]. Furthermore, a maximally functioning liver can clear ammonia only from that part of the cardiac output (30 per cent) that passes through it. In clinical situations in which ammonia is continuously entering the systemic circulation the arterial blood ammonia level will be elevated no matter how efficient the hepatic removal.

The foregoing observations have a bearing on the differences in the effect of L-arginine on ammonium salt administration as reported by Greenstein's group [16,17] and those presented

here. However, it is difficult to be certain how much of the difference should be attributed to the route and rate of ammonium and arginine administration, to the species utilized, and to the form of ammonium salt used. In their studies ammonium acetate was administered by a single intraperitoneal injection to rats fasted twenty-four hours, and arginine was administered in a similar manner. Ammonium acetate was not used for these intravenous studies in man because its hemolytic action *in vitro* was more marked than that of ammonium citrate or chloride solutions. Although L-arginine is not described as a nutritionally "essential" amino acid for adult rats or for man [18], a greater need for exogenous L-arginine in the twenty-four-hour fasted rat to participate in the metabolism of exogenous ammonia might contribute to the difference between the ammonia studies in rats and in man. Furthermore, intraperitoneal injection of ammonium salts differs from administration by other routes which deliver ammonia directly and continuously into the systemic circulation. With intraperitoneal administration much of the ammonia absorbed from the peritoneal cavity would be expected to enter the portal circulation and thus be exposed to the action of the liver before reaching the systemic circulation. This is a major difference from the clinical situations in man in which ammonia enters the general circulation without previous passage through the liver and in which only a portion of the circulating ammonia is exposed to possible removal by the liver.

Najarian and Harper reported improvement in the clinical state and fall in blood ammonia in all of fifteen patients with hepatic encephalopathy [19]. The reasons for the variance of their findings with those reported here are not readily apparent. L-Arginine HCl was given in approximately the same quantity and manner in both studies. However, they also gave 50 gm. of glucose simultaneously with the arginine, and several of their patients received two or three courses of arginine plus glucose. The role of glucose administration, of spontaneous variation in different patients, and of general medical care in producing the improvement in their patients is difficult to assess. In most of their cases, concomitant with arginine infusion, measures were taken to reduce the amount of ammonia being released from the intestinal tract into the circulation. Although in our patients with hepatic failure the cause was more fre-

quently neoplasm, many with extensive neoplastic invasion of the liver, it should be remembered that the subjects with normal liver function and elevated blood ammonia levels during controlled ammonium infusions also showed little or no response to L-arginine administration. Similarly, a recent report of observations in two subjects with and two without hepatic disease, indicated little effect of L-arginine on the blood ammonia elevations induced by ammonium chloride infusions [20].

In sixteen experiments in dogs, preliminary to these clinical studies, L-arginine also had no appreciable effect on the blood ammonia elevation induced by intravenous ammonium chloride infusions. Amounts of L-arginine were used which were comparable to or greater than those needed to prevent the ammonia rise and lethal effects in dogs following infusion of an arginine-free L-amino acid mixture [3].

The observation that arterial blood levels of ammonia more accurately reflect the status of the liver than do venous levels is in agreement with previous reports [21,22]. The observations here, however, are too few in number to suggest a correlation between the blood ammonia level or arteriovenous difference and the stage of hepatic encephalopathy. Of note in this regard is the finding with infusions of ammonium chloride, that blood ammonia levels greater than those found in patients with hepatic encephalopathy, though maintained up to four hours in subjects without liver disease, were not associated with the signs or symptoms of hepatic encephalopathy. Similar observations have been reported by Seegmiller et al. [23].

The finding of a normal peripheral A-V ammonia difference is of interest. McDermott, Adams and Riddell have previously demonstrated in man that portal and renal venous blood have a higher ammonia content than arterial blood [24], but ammonia release in the peripheral tissues has not been emphasized. In studies utilizing the Conway method for ammonia determination no peripheral A-V difference was found [22]. Because the identity of the substances contributing to blood "ammonia" as it is usually determined are not known, additional comment on these observations seems unwarranted at the present time.

In contrast to the normal situation is the reversed A-V difference, indicating peripheral removal of ammonia, when the arterial ammonia level is elevated as in hepatic failure or during

ammonium salt or glycine infusion. A similar correlation between arterial concentration and cerebral and peripheral A-V ammonia differences has been reported by Bessman who has discussed possible means of ammonia removal in peripheral tissues [25]. These mechanisms of ammonia removal apparently do not require arginine, and are capable of removing large amounts of ammonia when the blood levels are elevated [4,25].

Our present concept of the arginine-ammonia relationship emphasizes the important role of L-arginine in preventing toxicity and blood ammonia rise during amino acid administration and that its marked effect seems to be largely attributable to removal of the hepatic source of ammonia. Arginine and the Krebs urea cycle are also important in removal of ammonia from the blood. In a poorly nourished patient in whom arginine deficiency might contribute to an elevated ammonia level correction of such a deficiency would be important. However, at the present time efforts to reduce elevated blood ammonia levels of clinical significance seem to be more effective when directed at the source of ammonia rather than at ammonia removal sites. When the blood ammonia source in man is exogenous, L-arginine appears to be of limited clinical usefulness. This conclusion is tentative, and final evaluation of L-arginine in the therapy of hepatic encephalopathy and other disease states associated with high blood ammonia awaits further controlled clinical trial.

CASE REPORTS

CASE I. V. M., a fifty-two year old Negro woman, with carcinoma of the breast and metastases to the liver, had been treated by oophorectomy and adrenalectomy. On December 22, 1955, her liver was palpable 5 cm. below the right costal margin in the mid-clavicular line and she exhibited Stage III hepatic encephalopathy. L-Arginine was given without clinical improvement. She died on January 6, 1956. At autopsy the liver weighed 2,900 gm. and was largely replaced by tumor. Multiple small tumor deposits were found in the brain.

CASE II. M. L., a sixty year old Negro man, with hepatoma and without previous history of hepatic disease, had a liver palpable 20 cm. below the right costal margin and no evident collateral channels. At this time, January 12, 1956, L-arginine was administered. There was no improvement in the Stage II encephalopathy. The patient died on January 13, 1956. In the liver, tumor, portal cirrhosis and active chronic pericholangitis were seen.

CASE III. B. H., a sixty-eight year old white man, with acute myeloblastic leukemia without previous history of hepatic disease, was undergoing treatment with methotrexate and 6-mercaptopurine. He had Stage III encephalopathy without a palpable liver on April 10, 1956. L-Arginine was administered without improvement and by the following day the encephalopathy had progressed to Stage IV. The patient died on April 12, 1956, with *Pseudomonas* septicemia. At autopsy the liver weighed 2,000 gm. and showed inspissated bile in the biliary canaliculi and some areas of focal necrosis but no evidence of viral hepatitis or extensive infiltration with malignant cells. No encephalitis or leukemic infiltration was seen in the brain.

CASE IV. M. W., a forty-six year old white woman, with carcinoma of the breast and metastases to bone and liver, had a liver palpable 16 cm. below the right costal margin, and was in Stage II encephalopathy. At this time, on October 9, 1956, L-arginine was administered without improvement. The patient died three hours after the infusion. The liver at autopsy weighed 2,875 gm. and was extensively replaced by tumor.

CASE V. J. R., a forty-seven year old white man, with malignant carcinoid tumor of the cecum and liver metastases, had viral hepatitis three months following a blood transfusion. On December 5, 1956, the liver was palpable 5 cm. below the costal margin and Stage III encephalopathy was present. L-Arginine was infused without clinical improvement. The next day Stage IV encephalopathy was evident. The patient died on December 10, 1956. At autopsy the liver weighed 2,090 gm. and revealed several nodules of carcinoid tissue and extensive hepatic destruction characteristic of acute viral hepatitis.

CASE VI. F. H., a forty-one year old white woman, with carcinoma of the breast and liver metastases, had been treated with radical mastectomy and hypophysectomy. On January 10, 1957, the patient exhibited Stage I encephalopathy and had a liver palpable 10 cm. below the costal margin. She received L-arginine without improvement. On January 11, 1957, the patient died. At autopsy the liver was found to weigh 3,060 gm. and consisted of approximately 90 per cent tumor.

CASE VII. M. G., a thirty-two year old white woman, with carcinoma of the breast and liver metastases, had been treated with oophorectomy and hypophysectomy. On February 18, 1957 the patient was dehydrated, the liver was palpable 6 cm. below the costal margin, and Stage II encephalopathy was evident. L-Arginine was administered without clinical improvement. Two days later, with hydration and oral antibiotics, the encephalopathy had partially cleared (Stage I). A similar

change from Stage II to I occurred on February 25 and 26 without L-arginine administration. The patient died March 6, 1957. At autopsy the liver weighed 2,270 gm., 80 per cent of which was replaced by tumor.

CASE VIII. D. R., a fifty-eight year old woman, with a nine year history of intermittently progressive hepatic disease thought to be a residual of infectious hepatitis, had ascites, spider angiomas, esophageal varices, a non-palpable liver and Stage II encephalopathy. On March 6, 1957, L-arginine was administered without evidence of improvement. The patient died on March 15, 1957. At autopsy the liver, which weighed 1,100 gm., showed portal cirrhosis with bile stasis and active chronic pericholangitis.

SUMMARY

1. In patients with severe liver disease the arterial blood ammonia level was usually found to be greater than the venous level. This was not observed in subjects free of liver disease. The arterial blood ammonia level was found to be a better indication of the hepatic status than the venous blood ammonia value.

2. L-Arginine administered intravenously to eight subjects with advanced liver disease and hepatic encephalopathy did not produce any consistent clinical improvement or lowering of the blood ammonia. L-Arginine was similarly without significant effect when blood ammonia elevation was produced in subjects with normal liver function by exogenous (intravenous) administration of ammonium salts. These findings contrast with the marked effect of L-arginine in reducing the blood ammonia rise resulting from intravenous infusion of glycine or of an arginine-deficient L-amino acid mixture to fasted subjects.

3. The significance of these findings is discussed and it is concluded that L-arginine plays an important role in preventing or reducing elevated blood ammonia levels when it acts at the site of ammonia release. After intravenous administration of certain amino acids L-arginine acts through the Krebs urea cycle to prevent ammonia formation in the liver and release into the blood. However, L-arginine administration appears to be of limited value in reducing elevated blood ammonia levels when the ammonia source is primarily exogenous, as in most instances of hepatic encephalopathy or during intravenous administration of ammonium salts.

Acknowledgments: The authors wish to thank Dr. L. B. Thomas for review of the autopsy

material, Miss Patricia McCoy for her technical assistance and Mr. Milton Skolaut and the pharmacy staff of the Clinical Center, National Institutes of Health for their valuable assistance in the preparation of solutions.

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Allergy to Chlorpromazine Manifested by Jaundice*

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FEW drugs in medicine have been so widely used in so short a time as chlorpromazine. Soon after introduction of the compound the allergenic potentialities for some patients became evident. Urticaria or angioneurotic edema developed in 5 per cent of 283 patients treated with the drug for more than one week [7]. Maculopapular eruptions, erythema multiforme and exfoliative dermatitis have also been noted [2]. Contact dermatitis confirmed by patch tests has occurred among nursing personnel handling the drug [3]. Other reactions, possibly of allergic origin, include drug fever, photosensitive dermatitis, asthma and agranulocytosis. Although intrahepatic obstructive jaundice has been reported in as many as 4 per cent of some groups of patients treated with chlorpromazine, the over-all incidence in patients treated for at least a week is probably between 1 and 2 per cent [4].

Jaundice is not a common manifestation of drug allergy but it has been produced by a wide variety of agents. Jaundice that is clinically and histologically similar to the biliary disturbance caused by chlorpromazine has been observed following administration of arsphenamine [5], methyltestosterone [6], thiouracil [7] and cinchophen [8]. Hepatitis with hepatocellular damage, probably on an allergic basis, has been reported from administration of para-aminosalicylic acid [9], diethylstilbesterol [10], phenobarbital [11] and sulfadiazine [12].

Several circumstances support the belief that jaundice due to chlorpromazine is a manifestation of allergy. The incidence is comparable to that of other allergic disorders in the general population. In one report of 880 patients in whom jaundice developed from chlorpromazine the symptoms appeared in 80 to 90 per cent within the first four weeks of treatment and in 45 to 50 per cent between the first and third

weeks [4]. The time of onset in these patients is highly suggestive of an allergic reaction. Eosinophilic infiltration in the periportal spaces has been frequently described [13,14], as has eosinophilia of the peripheral blood [15]. The usually prompt recurrence of jaundice upon challenge with the drug also suggests an allergic mechanism [14,16].

In treating over 900 patients with chlorpromazine we discovered jaundice in seventeen cases. This report describes the clinical picture seen in these patients, an attempt to evaluate specific treatment, a short-term follow-up study, and an investigation of the role of allergy in the production of this complication.

RESULTS OF STUDY

Clinical and Laboratory Features. Chlorpromazine was administered to thirteen of seventeen patients for treatment of mental disorders, to three patients for relief of pain, and to one patient to determine its effect on essential hyperlipemia. All patients were men, whose ages ranged from twenty-four to seventy-five years. Only two were known to have had definite liver disease, one having had viral hepatitis four years earlier, and one with liver metastases as revealed by later autopsy. One other patient had been studied because of possible liver enlargement five years earlier but no abnormalities were found in the hepatic tests. Excellent documentation of possible exposure to hepatotoxic or icterogenic agents was afforded in sixteen patients who had been hospitalized for some time prior to the development of jaundice. None had been exposed to such agents. None of the patients suffered from any clinical allergy, but two had a history of previous sensitivity to drugs, one to penicillin and one to phenolphthalein.

The clinical features of chlorpromazine jaundice in these seventeen patients are sum-

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marized in Table I. At the dosage level used in these patients the dose of drug had little relation to the appearance of jaundice. Duration of treatment was more important, all cases occurring between seven to thirty-five days after beginning treatment.

Despite the fact that many of these patients were neither alert nor communicative, prodromal symptoms of fever, vomiting, diarrhea, abdominal pain or malaise were detectable in fifteen cases from one to seven days prior to the appearance of jaundice. As in the case of viral hepatitis, the patients often seemed to improve clinically with the appearance of jaundice. Pruritus was not a frequent symptom in these uncomplaining patients. Neither was liver tenderness or enlargement, which was present in only a few instances.

The jaundice was usually of mild degree, the highest level of serum bilirubin being 14.2 mg. per 100 ml. Direct-reacting bilirubin rose proportionately more than the indirect. Signs of cholestasis (elevation of serum alkaline phosphatase activity and serum lipids) were frequently noted. No correlation between the rise in serum alkaline phosphatase and the level of serum bilirubin could be found. The highest elevations of alkaline phosphatase (27, 22 and 18 Bodansky units) were associated with serum bilirubin values of 2.4, 4.4 and 1.9 mg. per 100 ml., respectively. The highest levels of serum bilirubin (14.2 and 9.5 mg. per 100 ml.) were associated with rises in alkaline phosphatase activity to 12.4 and 9.8 Bodansky units, respectively. Serum cholesterol was elevated initially (312 to 492 mg. per 100 ml.) in four of nine patients in whom determinations were made. Three patients with normal initial levels showed sharp rises during the course of the jaundice. The serum esterified cholesterol was usually reduced, the lowest value being 55 per cent. Serum phospholipids rose in the same manner as cholesterol. Flocculation tests were positive more often than anticipated. The cephalin flocculation test was sometimes positive when the thymol flocculation test was not. The positive tests were usually transient. Five of six patients with positive flocculation tests were among the seven oldest patients studied and three were in poor general health (two had metastatic carcinoma and one was severely undernourished). Although no diligent search was made, eosinophilia was found in four patients, with values of 6, 9, 19 and 22 per cent. The total leukocyte

count remained within normal limits in these cases. The duration of jaundice varied from three to forty days.

Effects of Treatment. Adrenocortical hormones or antihistaminics were given to seven patients at the onset of jaundice. Two patients received

TABLE I
CLINICAL CHARACTERISTICS OF CHLORPROMAZINE
JAUNDICE IN SEVENTEEN PATIENTS

Data	Patients (no.)
Daily dose of drug at onset of jaundice (mg.):	
100-150.....	4
200-250.....	6
300-350.....	3
400 or more.....	4
Duration of treatment prior to jaundice (days):	
7-13.....	6
14-20.....	4
21-30.....	6
over 30.....	1
Prodromal symptoms:	
Total with symptoms.....	15
Fever.....	13
Gastrointestinal symptoms.....	11
Malaise.....	7
Highest total serum bilirubin (mg. per 100 ml.):	
1.5-2.9.....	7
3.0-5.9.....	5
6.0 or more.....	5
Mean value 4.8	
Highest alkaline phosphatase (Bodansky units):	
Not recorded.....	2
4.0-5.9.....	1
6.0-7.9.....	2
8.0 or more.....	12
Mean value 12.4	
Flocculation tests:	
Cephalin flocculation >2+ in 48 hr.....	6
Cephalin flocculation <2+ in 48 hr.....	10
Thymol flocculation positive.....	4
Thymol flocculation negative.....	12
Not recorded.....	1
Duration of jaundice (days):	
7 or less.....	4
8-14.....	4
15-21.....	4
22-30.....	1
30 or more.....	4

cortisone, four received prednisone, and one received diphenhydramine. In each case the dose of cortisone was 100 mg. daily, of prednisone 80 mg. daily, and of diphenhydramine

TABLE II
HEPATIC TESTS AT FOLLOW-UP EXAMINATION OF ELEVEN PATIENTS WITH JAUNDICE FROM CHLORPROMAZINE

Case	Duration of Follow-up Period (months)	Hepatic Tests at Follow-up Examination					
		Total Serum Bilirubin (mg. per 100 ml.)	Cephalin and Thymol Flocculation Tests (48 hr.)	Bromsulphthalein Retention, 5 mg./Kg./45 min. (%)	Serum Cholesterol and Esters (mg. per 100 ml.)	Serum Albumin/Globulin (gm. per 100 ml.)	Thymol Turbidity (units)
I, H. G.	4	0.51	Cephalin 4+ Thymol negative	4.2	242 (70%)	4.4/3.2	6.5
II, C. H.	5	0.46	Negative	4.5	195 (70%)	4.4/3.0	5.1
III, M. G.	6	0.47	Negative	13.3	260 (77%)	4.6/3.0	1.7
IV, A. H.	13	0.40	Negative	3.4	280 (74%)	3.6/2.7	3.2
V, A. G.	14	0.51	Negative	3.4	231 (74%)	3.9/3.8	1.1
VI, E. W.	14	0.53	Negative	3.0	277 (74%)	4.0/3.7	2.3
VII, J. S.	16	0.80	Negative	4.1	268 (68%)	4.9/2.5	2.0
VIII, D. W.	16	0.25	Negative	1.2	275 (77%)	4.8/3.8	4.8
IX, W. B.	28	0.32	Negative	3.4	251 (74%)	5.2/3.2	2.0
X, J. G.	20	0.40	Cephalin 4+ Thymol negative	245 (71%)	6.0/2.8	...
XI, J. M.	25	0.63	Negative	17.5	252 (74%)	5.3/3.1	3.2

400 mg. daily for at least seven days followed by tapered doses during an additional two weeks of treatment or until jaundice had subsided. Eight patients received no specific treatment and two patients continued to receive either the same or an augmented dose of chlorpromazine after the onset of jaundice.

The average duration of jaundice was twenty days in seven patients who received specific treatment, and sixteen days in eight patients who received no specific treatment. Before any conclusions are drawn, it should be mentioned that the patients treated were somewhat more deeply jaundiced as a group than those untreated, which probably accounted for the longer clearing time for the group treated. Jaundice persisted for thirty-four and thirty-five days in the two patients who received the drug without interruption. Continued treatment with chlorpromazine did appear to prolong jaundice, although both patients had metastatic carcinoma and were in poor general health.

Results of Follow-up Studies. After the occurrence of jaundice, eleven patients were followed up with serial hepatic tests for from four to twenty-five months and eight patients for more than a year. The results of the final tests are listed in Table II. Other hepatic tests were performed

but the tests tabulated were selected for presentation because they were deemed more likely to indicate any parenchymatous liver damage. Tests indicating biliary obstruction (increased direct-reacting serum bilirubin, bilirubinuria, increased serum alkaline phosphatase activity, or elevation of serum lipids) or its release (increased urobilinogenuria) were most frequently abnormal but returned to normal promptly, even in cases not included in the follow-up study.

The cephalin flocculation test remained positive in two patients, despite the fact that the thymol flocculation test was persistently negative in both. H. G. (Case I) escaped from the hospital before longer follow-up study could be completed. The positive flocculation test in J. G. (Case X), who had essential hyperlipemia, was ascribed to his lipemic serum. This serum also interfered with determinations of bromsulphthalein retention and thymol turbidity.

The abnormal retention of bromsulphthalein in M. G. (Case III) was still present four months after he had reacted positively to a challenge dose of chlorpromazine. This test was still abnormal in J. M. (Case XI) eight months after his second attack of jaundice. Seventeen months after his first episode, dye excretion had been determined as normal.

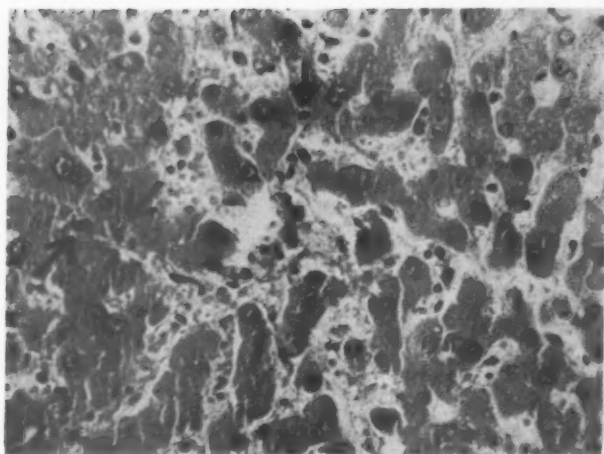


FIG. 1 Liver from patient treated with chlorpromazine 300 mg. daily through course of jaundice. Jaundice subsided in thirty-five days, hepatic tests normal at time of death thirteen months later. Note bile plugs in canaliculi (arrows), collapsed central vein and pleomorphic nuclear changes. Hematoxylin and eosin; original magnification, $\times 370$.

Normal values for total and esterified cholesterol, according to the technic used for measurement, were obtained in all cases. The lowest serum albumin levels, in A. H. (Case iv) and A. G. (Case v), were associated with poor nutrition in each case. Borderline values for thymol turbidity were found in Cases i, ii and viii. H. G. (Case i) had been followed up only a short time, but a liver biopsy taken during the course of his jaundice did not show any significant hepatocellular damage. C. H. (Case ii) had previously had viral hepatitis, and D. W. (Case viii) had coexisting diabetes. Although striking abnormalities of hepatic tests were rare, three of these eleven patients were definitely abnormal in one or more respect.

Both patients with carcinoma ultimately died. The first patient (Case iv in Table ii) continued to receive a daily dose of 300 mg. of chlorpromazine for thirteen months after jaundice developed. The second patient (not documented in Table ii since he survived only a month after the onset of jaundice) continued to receive 300 mg. of chlorpromazine daily until his death. In each case the primary diagnosis of malignancy was justification for continued use of the drug.

Postmortem examinations were made on both patients with carcinoma. In the first case the liver was of normal size without metastatic involvement. On microscopic examination, the central veins were found to be collapsed, bile plugs were still present in canaliculi, and pleomorphic nuclear changes were seen in some



FIG. 2. Same case as Figure 1. Finely vacuolated fat deposit in periphery of lobules. Oil red O; original magnification, $\times 33$.

hepatic cells. (Fig. 1.) Fat stains revealed the presence of finely vacuolated fat deposit in the periphery of the lobules. (Fig. 2.) This deposit was thought to be more likely due to toxic factors than to nutritional factors.

The liver in the second case had numerous nodular metastases and weighed 2,500 gm. The parenchyma between metastases showed moderate accentuation of the lobular markings. Sections of liver, well removed from areas of metastasis, showed marked changes of a toxic type. Marked lobular distortion with increased connective tissue, cellular infiltration and striking proliferation of bile ducts were seen. (Fig. 3.) Hepatic cells showed evidence of severe damage with vacuolization. Numerous large bile plugs were found. (Fig. 4.)

Due consideration was given to the fact that both patients were poorly nourished and affected by malignant disease. The second patient had also been treated for pernicious anemia prior to the development of gastric malignancy. However, the histopathologic changes in each patient were still thought to be chiefly of toxic origin. One cannot be certain that such evidence of toxic hepatitis would have occurred in patients in good general health who had continued to receive chlorpromazine following the appearance of jaundice.

Role of Allergy in the Production of Jaundice. Skin tests to demonstrate allergy to chlorpromazine were made in twelve patients during or following an attack of jaundice, in twenty-five patients who had never had the drug, and in thirty-five patients who had received from 100 to 1,600 mg. of the drug daily for varying periods

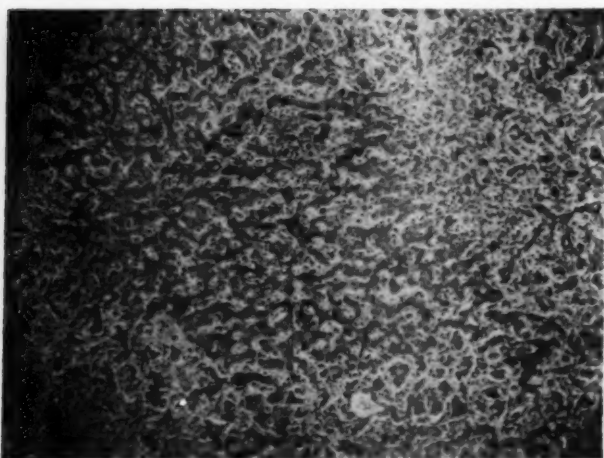


FIG. 3. Liver from patient treated with chlorpromazine 300 mg. daily through course of jaundice. Jaundice subsiding, hepatic tests improving at time of death thirty-four days after onset. Note marked lobular distortion with increased connective tissue, bile duct proliferation and cellular infiltration. Hematoxylin and eosin; original magnification, $\times 100$.



FIG. 4. Same case as Figure 3. Large bile plug. Vacuolated hepatic cells Hematoxylin and eosin; original magnification, $\times 370$.

of time without evidence of sensitization. (Table III.)

Each patient was patch-tested for forty-eight hours with a 3 per cent aqueous solution of the drug. These patch tests were uniformly negative.

Intradermal tests were administered with 0.1 ml. each of antigens containing 0.1 mg. per ml. and 0.5 mg. per ml. in saline solution and 0.5 mg. in serum. Two types of the serum antigen were used. The first was prepared in a fashion similar to that of an antigen which successfully demonstrated cutaneous sensitivity in three patients with amidopyrine agranulocytosis [17]. Chlorpromazine and serum were mixed, passed through a Seitz filter, and stored at 4°C. for several days. The second type was prepared in the same way without filtration and with storage at room temperature. A slight precipitate formed when this amount of drug was mixed with the serum. Increased concentrations of chlorpromazine produced even greater precipitation, precluding the possibility of preparing a stronger antigen of known concentration.

The intradermal tests were quite variable and difficult to interpret. The weaker preparation in saline solution produced immediate reactions varying from no visible wheal to wheals 10 mm. in diameter in all groups tested. The stronger preparation in saline solution produced wheals more frequently and generally of larger average size, suggesting that much of the reaction was produced by non-specific irritation. Reactions were alike to both types of serum antigens. In

most instances the wheals formed in response to comparable antigens in saline solution and serum were similar, but in twelve cases the differences were great enough to make interpretation equivocal. Six of these equivocal results were obtained in patients receiving the drug without earlier or subsequent signs of sensitization, three in patients with previous jaundice, and three in patients never receiving the drug. Erythema and pseudopod formation surrounding the wheal, so characteristic of genuinely positive cutaneous tests, was lacking in these equivocal tests. No delayed reactions occurred.

The most successful, and also the most hazardous, method for demonstrating drug allergy is re-administration of the suspected agent (challenge test). Eleven patients with jaundice due to chlorpromazine therapy were challenged with the drug from ten days to seventeen months after the initial episode of jaundice. The challenge dose, usually comparable to that which the patients received when jaundice first developed, ranged from 100 to 300 mg. daily. Clinical jaundice was reproduced in six patients. Two patients had fever and gastrointestinal symptoms accompanied by increase in bromsulphathlein retention and serum alkaline phosphatase activity, but were without clinical jaundice. In one patient fever and vomiting occurred, but hepatic tests were not obtained. Two patients showed no reaction to the challenge. When symptoms were produced they occurred within the first twelve to twenty-four hours and jaundice was evident by forty-eight hours after the first challenge dose. At the first appearance of symptoms the drug was discontinued, usually

after the second or third dose. None of the patients was re-treated for longer than forty-eight hours.

Recurrences of jaundice were produced as early as ten days and as late as seventeen months after the initial attack. On the other hand, some

TABLE III
RESULTS OF TESTS FOR ALLERGY TO CHLORPROMAZINE

Patch tests—3% solution for 48 hours:	
12 patients previously jaundiced	All negative
25 patients never received the drug	All negative
35 patients currently receiving the drug	All negative
Cutaneous tests—0.1 ml. of 0.05% solution in serum compared with 0.1 ml. of 0.05% solution in saline solution:	
12 patients previously jaundiced	3 equivocal reactions
25 patients never received drug	3 equivocal reactions
35 patients currently receiving drug	6 equivocal reactions
Challenge dose of drug—11 patients previously jaundiced:	
Prompt recurrence of clinical jaundice	6
Prompt recurrence of prodromal symptoms and abnormal hepatic functions tests	2
Prompt recurrence of prodromal symptoms (hepatic tests not obtained)	1
No change	2

patients apparently lost their sensitivity to the drug as early as three weeks following the first episode. In all but one case the second episode of jaundice was milder than the first, both in degree and duration. One patient, after two mild episodes of jaundice, was started on the drug for a third time, using initial daily doses of 25 mg. followed by cautious increments of 25 mg. daily. He finally could be maintained on 150 to 200 mg. of chlorpromazine daily for several months with no evidence of recurrent jaundice or impaired liver function. Two patients who had already had two episodes of jaundice were treated inadvertently with the drug for the third time. In one a third frank episode of jaundice developed, in the other fever and malaise developed but there was no frank jaundice. Treatment

of both patients was promptly stopped when symptoms recurred.

Promazine, a drug with many actions similar to chlorpromazine, is identical in chemical structure except that the phenothiazine ring is not chlorinated. An attempt was made to see if cross-sensitization occurred between these two drugs. Three patients who had had a second episode of jaundice following challenge with chlorpromazine were given a course of promazine within a few weeks after the second episode. In none did untoward symptoms, abnormal hepatic tests or jaundice develop while receiving promazine. Two of these patients, as already mentioned, were treated with chlorpromazine a third time, both showing evidence of retained sensitivity.

Four additional patients who had jaundice after chlorpromazine therapy were studied. A course of promazine was administered to these patients. No clinical symptoms appeared and hepatic tests were unchanged during the test period. Without interruption of medication, they were switched to chlorpromazine. In one patient clinical jaundice developed, two patients had fever, gastrointestinal symptoms and abnormal hepatic tests, and one remained unchanged. These tests were believed to demonstrate that there was no cross-sensitivity between these two closely related phenothiazine drugs.

COMMENTS

The appearance of fever, gastrointestinal symptoms and malaise during the first four or five weeks of chlorpromazine treatment should alert the physician to the possibility of jaundice. Even though the drug is discontinued at this point, jaundice may still occur [18,19]. If hepatic tests indicate that the jaundice is of the obstructive type, a diagnosis of jaundice due to chlorpromazine therapy can almost certainly be made. So characteristic is the clinical picture that an erroneous diagnosis is unlikely. However, failure to remember that the patient had received chlorpromazine or that jaundice may be preceded by prodromal symptoms occasionally led to erroneous diagnoses in our cases. Influenza or gastroenteritis were the first diagnoses in four of our patients before jaundice developed. One patient with the prodromal symptoms and clinical jaundice was thought to have viral hepatitis before the laboratory tests were obtained. A diagnosis of carcinoma of the pancreas was entertained in one patient with metastatic

carcinoma in whom the primary site of the tumor had not been determined. Only when jaundice began to clear rather than deepen did a retrospective study show that he had been started on chlorpromazine three weeks before jaundice developed.

Abdominal pain may be colicky and most severe in the upper right quadrant. The combination of upper abdominal pain, fever and obstructive jaundice has led to surgical intervention in a number of cases [20-22]. Such needless operations might have been prevented had inquiry been made about the use of chlorpromazine in the preceding month.

Much mystery and some confusion has resulted from trying to establish the exact incidence of jaundice from chlorpromazine. The mystery originated in the discrepancies in various reports of frequency. Confusion has arisen because the incidence may vary with the type of patient population under treatment. Young patients in good health seem less susceptible to drug allergies than old patients in poor health. Then, too, it would appear that in most cases at least one week of continued treatment with the drug is required to produce sensitization. In patients treated for only a few days this complication is not likely to develop.

Aside from differences among patients, two other factors may add to the difficulty of determining the exact incidence of jaundice. First, in some of the cases jaundice was mild (serum bilirubin values of 2 mg. per 100 ml. or less) and of short duration (from three to seven days). One must be alert to discover these patients, especially if they are stoical psychotics. Apparently, jaundice does not deepen with continued treatment and clears with only slight delay. Thus continued use of the drug in an undetected case is not likely to enhance the prospects for discovery. Second, it has been well documented that "hepatitis," manifested by enlargement or tenderness of the liver, fever, abnormal liver function tests or histologic evidence of "allergic cholangiolitis," may occur without clinical jaundice [23,24]. Such cases should be included among those of chlorpromazine jaundice but may easily be missed if medical supervision of patients is not vigilant.

Jaundice from chlorpromazine usually runs a self-limited course which is briefer than that of viral hepatitis, with only a few exceptions [20]. During the acute course liver biopsies usually show only minimal hepatocellular damage.

Follow-up examinations have been too few to permit firm conclusions. One study, based on biopsy material, has raised the possibility of permanent parenchymatous damage [25]. On the other hand, examination of the liver of patients who have died from other causes following chlorpromazine jaundice indicates a course tending toward healing [26]. After an estimated four million patients had been treated with the drug, only twenty-six deaths had been reported in patients with jaundice. Of these, the drug was thought to be responsible in thirteen cases [4]. Most of the fatal cases have been complicated by other conditions, such as concurrent agranulocytosis, heart failure, possible viral hepatitis or cirrhosis, or recent surgery. One death with acute hepatic necrosis occurred in an eighty-one year old mental patient [27]. The present study seems to indicate that there is a definite hazard of permanent liver damage if patients are re-treated following an attack of jaundice or if treatment is continued without interruption. The tendency of some therapeutic enthusiasts to resume or continue treatment despite the appearance of jaundice is to be deplored unless there are definite extenuating circumstances.

Although treatment with bed rest, increased diet and nutritional supplements has been uniformly recommended for patients with jaundice caused by chlorpromazine, such recommendations appear to have been made from force of habit rather than from clear-cut evidence of benefit. No severe restriction in activity or change in diet was recommended in our patients, with no apparent deleterious effects. Because of reports of the amelioration of methyltestosterone jaundice by adrenocortical hormones, this treatment has been used in patients with chlorpromazine jaundice. While an occasional patient shows what appears to be a clear-cut improvement from adrenocortical hormones [14,28], the results of our studies provided no convincing proof that these agents altered the natural course of the illness. Such treatment should probably be reserved for the more severely jaundiced patients. The use of hydrocholeretic agents, such as sodium dehydrocholate, is contraindicated since hepatic bile secretion is stimulated while there is no adequate avenue of release [14].

Drug allergy is difficult to establish as the cause of any systemic illness. The difficulty lies in the fact that most technics for the demonstration of allergy fail in the case of drugs. Challenge

with the suspected drug is the best method for demonstrating drug allergy. Nine of eleven patients challenged in this study demonstrated objective evidence of sensitivity to chlorpromazine even for periods as long as seventeen months after an attack of jaundice. Other studies have also reported successful reproduction of jaundice upon challenge with chlorpromazine [14,16]. When one bears in mind the numerous other clinical manifestations of chlorpromazine sensitivity, the narrow time-range for development of jaundice, the lack of influence of dosage level, and the characteristic tissue response, the probability that jaundice is due to drug allergy appears to be high. Although extensive toxicity studies in animals have failed to reveal hepatic damage after large doses and prolonged use of chlorpromazine [29], continued use of the drug in sensitized patients appears to lead to permanent toxic changes in the liver.

Since the number of phenothiazine derivatives with potential clinical importance is ever enlarging, the possibility of cross-sensitization among drugs of this series arises. Cross-sensitivity has been proposed as the explanation for one case in which jaundice followed a single dose of 50 mg. of chlorpromazine [16]. The supposition was that the patient had previously received promethazine. Although in this patient jaundice promptly developed when challenged with chlorpromazine several months later, no attempt was made to reproduce jaundice with promethazine.

No cross-sensitization with promethazine, diethazine or two other phenothiazine derivatives was seen in patients with contact dermatitis from chlorpromazine and positive patch tests to the latter drug [3]. In the present study cross-sensitivity to promazine could not be demonstrated, even in patients who still retained their sensitivity to chlorpromazine.

At present, the mechanism by which chlorpromazine allergy produces jaundice can only be surmised. Much of the drug is eliminated in the bile, where it probably attains a significant concentration. From 9 to 15 per cent of a single intraduodenal dose of the drug was excreted in the cannulated bile of dogs within the first eight hours [4]. After repeated oral doses have been given first, the biliary excretion of the drug is greatly increased. Judging from the characteristic histologic picture a reaction is produced in the biliary radicles which results in

cellular infiltration in the portal spaces and the formation of bile plugs. Just how these plugs are formed is a matter of conjecture. Addition of small amounts of chlorpromazine to a protein-containing fluid, as in the case of our serum antigen, does produce a precipitate. No such precipitation is observed in the cannulated bile of dogs because the drug is eliminated as a soluble complex and no inflammatory exudate is present. In any case, the biliary block occurs in the smaller radicles. There is little evidence to support the idea that jaundice might be produced by increased resistance of the choledochoduodenal sphincter from the pharmacologic action of large doses of the drug [30]. Such biliary stasis can be produced only in cholecystectomized animals and might be equally well produced by a number of drugs, of which morphine would probably be one.

As yet there is no convenient method for determining in which patients chlorpromazine jaundice is likely to develop. Cutaneous tests for sensitivity appear to be valueless. Serial determinations of serum alkaline phosphatase activity have been proposed as a test; the findings become abnormal prior to the onset of clinical jaundice [31]. Seven patients of seventy studied in this fashion showed rises in alkaline phosphatase between the ninth and nineteenth days of treatment. The drug was discontinued in five patients in whom jaundice did not develop. In two patients who continued on chlorpromazine, jaundice appeared six to seven days after the first rise in alkaline phosphatase. Since in three patients in our study elevations of alkaline phosphatase did not develop beyond those usually found in hospitalized patients, despite the definite appearance of jaundice, baseline determinations would seem to be required. Screening patients by this method is hardly suitable for widespread application.

Routine testing of urine for the presence of bile aids detection of jaundice once it has occurred. Such a procedure might be feasible when medical observers are scarce or hospital lighting is poor (as it so frequently is). Daily temperature records and the prompt reporting of any untoward symptoms during the first month of treatment is the simplest and perhaps the most effective method for detecting possible trouble. Unless there is an urgent reason for continuation of the drug, the appearance of fever or systemic symptoms during this period should signal the cessation of treatment. Jaun-

dice may still occur, but early detection may lessen its severity.

The risk of jaundice from chlorpromazine has not been great enough in our experience to deter us from using the drug when indicated. The two major hazards of chlorpromazine jaundice are the risk of an unnecessary surgical procedure or the possibility of parenchymatous liver damage. The first can be avoided by asking all patients with obstructive jaundice about their recent medications or by using the biopsy needle before the knife. The second complication is not entirely avoidable. However, if the drug is not used in debilitated patients, if provision is made for close observation of the patient during the crucial first month, and if the drug is not re-administered to sensitized patients, the incidence of serious hepatic sequelae should be still further reduced.

SUMMARY

Seventeen cases of jaundice due to chlorpromazine were observed among over 900 patients treated with the drug. The clinical picture of fever, gastrointestinal symptoms and malaise, followed shortly by jaundice, occurred within the first four or five weeks of treatment. Enlargement or tenderness of the liver and pruritus were occasionally noted. Laboratory signs of obstructive jaundice were most commonly found. The usual clinical course was self-limited but continued use of the drug in sensitized patients may produce permanent liver damage.

The effect of treatment was equivocal but the use of adrenocortical hormones or antihistaminics should be considered in severe cases.

Prevention of this complication is difficult but prompt detection and discontinuation of the drug might make for a milder course. The risk of jaundice has been no deterrent to use of chlorpromazine when it is the drug of choice.

Drug allergy has been proposed as the cause of jaundice due to chlorpromazine. Cutaneous tests for detecting chlorpromazine allergy were unrewarding. However, nine of eleven patients challenged with the drug showed evidence of retained sensitivity for as long as seventeen months after the first appearance of jaundice.

No cross-sensitivity with promazine could be demonstrated, suggesting that other phenothiazine derivatives might be substituted in patients in whom sensitivity to chlorpromazine develops.

Acknowledgment: The author would like to express his appreciation to Dr. Virginia L. Cull for her help in the histopathologic studies.

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Familial Cholelithiasis, with Special Reference to Its Relation to Familial Pancreatitis*

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THERE has been a constant search for a single cause for gallstones. Infection, stasis and, more recently, chemical aberrations have been included as local factors [1,2,18]; hypercholesterolemia, hemolytic anemia, and possibly hyperlipemia have been mentioned as systemic factors [3,4]. Although there are certain obvious exceptions, the mechanism of stone formation in most patients submitted to surgery for this disease remains obscure.

There are a number of well known clinical facts about patients with gallstones. The largest incidence of gallstones is in women in the third and fourth decades, and pregnancy is said to increase the risk of having gallstones [5,6,7,8]. The familial incidence of gallstones has been noted, but it has been stressed that the occurrence has been predominantly among the women in each family group [9,10].

The following study was undertaken when one of the patients to be described (T. W.), was admitted to the hospital with a surgically proved acute and chronic pancreatitis. The family history strongly suggested that several other members of the family had chronic pancreatitis, and metabolic studies were accordingly undertaken. It was soon discovered that, although the history in several instances was typical of pancreatic pain, four of the seven members of the second generation had direct or indirect evidence of gallbladder disease. There were several features unusual for cholelithiasis including a high incidence in men as compared to women, and an early age of onset of symptoms (which is not rare in women but is very unusual in men [5,6,7,9]); there was also the question of the relationship of cholelithiasis to pancreatitis in these patients.

METHODS

A history was obtained relating to four members of the first generation, seven members of the second generation and thirteen members of the third generation. Detailed studies were made on the five members of the second generation who had symptoms and the two oldest members of the third generation who had symptoms. The studies performed included a complete physical examination and determinations of the hemoglobin, serum bilirubin, blood amylase [13a], blood lipase [13b], total serum lipids [13c], phospholipids [13d], total cholesterol and cholesterol esters. Biliary drainage was performed and the proteinase lipase and amylase activity of the duodenal fluid was determined [13e]. Fractional gastric analysis was carried out. Radiographic studies included film of the abdomen and x-rays of the gallbladder with a single and, if necessary, a double dose of dye.

CASE REPORTS

T. W., a forty-two year old man, was admitted to the hospital on May 14, 1956. Twenty-one years prior to this admission he began to have upper abdominal pain which radiated to his back. The pain would last from several hours to several days and was not usually related to meals. Nineteen years prior to admission his gallbladder was removed; he was told it was diseased but that it did not contain stones. After several months the pain recurred at infrequent intervals and for several months he had severe back pain, thought to be due to a ruptured intervertebral disc but this was never proved. He was relatively free from pain for seven years prior to admission but three weeks before he came to the hospital he again had upper abdominal pain and a spiking fever. Ten days prior to admission jaundice developed.

On admission physical examination and laboratory data were consistent with acute and chronic pancreatitis and suggested a complicating pseudocyst. The inflammatory process did not respond to medical treatment. The patient was explored and was found

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to have subacute and chronic pancreatitis but no pseudocyst. A T tube was placed in the common duct. His convalescence was slow but steady. Three months after the operation he had gained 30 pounds in weight and was free from pain.

F. W., a thirty-one year old man, began to have attacks of pain at the age of fifteen, sixteen years prior to his examination on June 29, 1956. There was sudden onset of severe epigastric pain lasting for one-half hour. This did not radiate to his back. A second similar episode occurred when he was seventeen years old, but lasted slightly longer. The first major episode came while he was in the Army, when he was approximately twenty years old. There was sudden onset of severe epigastric pain and abdominal pain in the left upper quadrant which radiated to the left scapular region. The pain lasted a week, and was associated with jaundice, dark urine, fever and light-colored stools. Since then the patient has had similar episodes every one or two years. The most recent attack occurred about ten weeks prior to his examination at this hospital. An x-ray of the gallbladder taken after his most recent attack was said to have shown no stones but stones were noted on examination at this hospital. In relation to the serum lipids, it should be pointed out that the patient had been given a low fat diet for two and one-half months prior to his visit to this hospital. The patient uses alcohol but has never noted a connection between this and his pain.

Physical examination was non-contributory. Laboratory data are set forth in the accompanying Tables I and II.

G. O., a forty-four year old woman, began to have attacks of severe epigastric pain which radiated to the interscapular region at the age of eighteen, twenty-six years prior to her examination at this hospital on June 29, 1956. These attacks lasted from several hours to several days and were accompanied by icterus, dark urine and light-colored stools on five occasions during that period. Even in the absence of jaundice the patient had noted that her stools were foamy during attacks. Gallbladder x-rays taken eleven years before the present examination were said to have shown no stones but she was told that there was "narrowing between the stomach and the bowel." Physical examination revealed no abnormalities except for slight epigastric tenderness. Data are shown in the Tables I and II.

J. W., a thirty-six year old man, was entirely well until eighteen months prior to his examination on June 12, 1956. At that time he was awakened at 3:00 A.M. by severe upper abdominal pain which radiated to the back at the level of the lower thoracic spine. The pain was described as steady and stabbing. It persisted for several hours, was associated with considerable nausea, and was not relieved until an injection

was given by his physician. Since then he has had several bouts of nausea but no pain. He thought that his stools of late may not have been as well formed as usual and perhaps foul smelling. There was no icterus. The patient uses small amounts of alcohol without relation to his pain. Physical examination revealed no abnormalities. Laboratory data are recorded.

F. W., a forty-one year old man, had typical biliary colic five years prior to his visit here on June 22, 1956. Cholecystectomy was performed but the common duct was not explored. Gallstones were present. Subsequently he had vague upper abdominal pain, and in September, 1956, jaundice developed. Operation revealed common duct stones which were removed. He has been free of symptoms since then. The pancreas appeared to be normal at the time of operation.

R. W., a nineteen year old boy, had had one episode of upper abdominal pain, lasting an hour and without radiation to the back. He had some upper abdominal distress when eating fatty foods. The history was non-specific, however physical examination was within normal limits. Data are given in the Tables I and II.

P. W., a seventeen year old girl has had cramping and aching abdominal pain for five years. The pain which persists for about an hour, is aggravated by taking fatty foods, and is somewhat relieved by bowel movement. Alcohol is not used. Physical examination was non-contributory. Laboratory data are shown in Tables I and II.

RESULTS

Some of the historical data and all the other data are recorded in Figure 1 and Tables I and II. Detailed histories were obtained only of the first generation, which included the mother of the group that was available for detailed chemical studies. There were three women and one man. All patients had jaundice at the time of their death. The mother of the second generation had abdominal pain and jaundice. She died following an abdominal operation for gallstones. The man in the group died of jaundice. This obviously does not prove the presence of cholelithiasis but at least in the women it suggests the presence of biliary tract disease.

Complete study of the biliary tree, including radiologic data in three individuals and operative findings in two, allows more definite conclusions in this group. Five of seven members of the second generation had proved biliary tract disease. Of these, four were men. The female member (G. O.) had cholesterol crystals in biliary drainage specimens and a non-function-

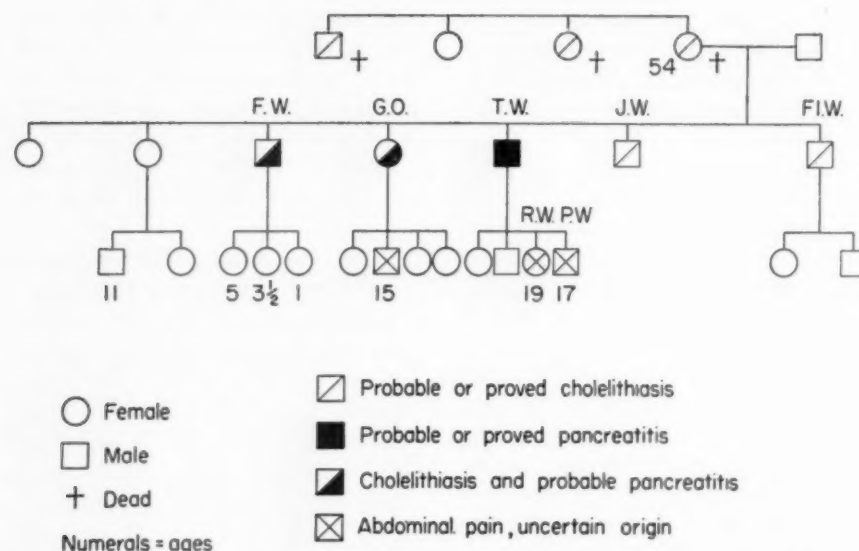


FIG. 1. Genealogical table of the reported family.

ing gallbladder with a single dose of dye. One of the patients (F. W.) had been operated upon three years before coming to this hospital and gallstones were found; later, common duct stones were removed at this hospital. The second man (T. W.) had had an operation for recurrent abdominal pain twenty years before the present hospitalization and at that time had been told he had a diseased gallbladder but no stones. He later had proved pancreatitis. The third man (J. W.) had no "B" bile on biliary drainage and no filling of the gallbladder with a double dose of dye. The fourth man had a gallbladder full of radiolucent stones. Thus five of seven members of the second generation had gallstones and of these, four were men; and eight of eleven members of the first and second generations had gallstones or suggestion of gallstones and of these, five were men. This is an unusually large proportion of men to women.

It is of interest that the average age of onset of symptoms in the second generation was 24.4 years. In three members of this group the pain started before the age of twenty. Although cholelithiasis is known to occur at an early age in women [5,7], the occurrence of symptomatic biliary disease before the twenties is rare in men [6,7,9].

Only two members of the third generation were studied because most representatives of this generation were very young. The two members studied had had upper abdominal pain of a non-specific nature; the boy had had one attack of severe abdominal pain, and the girl five years of rather diffuse upper abdominal pain. Biliary

drainage and radiographic study of their biliary tree showed no abnormality.

The evidence for pancreatic disease is not as secure in most of the patients. We have had the opportunity to obtain an amylase determination during an acute episode of pain in only one patient because we did not see the other patients during their attacks.

T. W. had a slightly elevated serum amylase but serum lipase was normal. A long history of pain with all the characteristics of pancreatitis, together with the absence of stones at the initial operation, suggest that pancreatitis was the original cause of his upper abdominal discomfort. The history of two other patients (F. W., G. O.) in this group suggested pancreatic pain [14,15]. The history of the other two patients in this generation had very little to suggest pancreatic disease. One other minor point in favor of pancreatic disease in the two patients with suggestive pancreatic pain was the presence of light-colored and foamy stools at the time they had episodes of discomfort.

Alcohol did not play an important role in any of the patients with possible pancreatitis but was taken in reasonably large quantities in the man with proved gallstones. This patient's pancreas was grossly normal at operation. There was no history to suggest hemolytic disease and a normal hemoglobin and lack of jaundice support this position.

The chemical features are of considerable interest. The serum lipase was elevated in all patients tested except for T. W., the patient operated upon for acute pancreatitis; the serum

TABLE I
BLOOD CHEMISTRY VALUES

Patient	Blood Studies				Lipids			
	Hemo- globin (gm. %)	Serum Bilirubin (mg. %) Direct/ Total	Serum Amylase (units)	Serum Lipase (units)	Total (mg. %)	Phospho- lipids (mg. %)	Cholesterol	
							Free (%)	Total (mg. %)
T. W.	12.7	0.6/1.4	217	60	861*	N.D.†	52	100‡
F. W.	14.4	0.16/34	40	240	300	N.D.	42	117
G. O.	13.1	0.13/0.41	118	200	420	N.D.	65	113
J. W.	14.8	neg./0.38	93	335	840	9.8	44	280
Fl. W.	13.8	neg./0.75	85	270	574	6.3	50	240
R. W.	13.4	0.10/0.25	85	265	364	6.4	40	160
P. W.	13.8	0.04/0.5	76	220	476	7.4	67	208
Normal values	80-180	80-180	861 ± 74	8.7 ± 0.6	76.2 ± 8.9	1.97 ± 20.2

* 2 mo. postsurgery with T tube in place.

† Not determined.

‡ Prior to surgery. 2 mo. postsurgery, serum total cholesterol 230 mg. per cent, of which 59 per cent were esters.

TABLE II
BILIARY DRAINAGE AND RADIOGRAPHIC DATA

Patient	Biliary Drainage				Gastric Analysis Units Free HCL†	X-ray of Gallbladder‡
	Microscopic*	Proteinase (units)	Amylase (units)	Lipase (units)		
T. W.	Positive	N.D.	N.D.	N.D.	12	No gallbladder
F. W.	Positive	N.D.	N.D.	N.D.	N.D.	Filled with radiolucent stones
G. O.	Equivocal§	22	276	21	0	No filling with single dose of dye
J. W.	No "B" bile	47	67	33	30	No filling with double dose of dye
Fl. W.	No "B" bile	41	81	30	30	No gallbladder
R. W.	Normal	82	31	28	56	Normal
P. W.	Normal	N.D.	N.D.	N.D.	N.D.	Normal
Normal values	45-185	50-165	46-147

NOTE: * Positive = pigment + crystals.

† Peak acid.

‡ Film was negative in each case.

§ Equivocal = crystals or pigment in small amounts.

|| Not determined.

amylase was normal in all cases save the last-named patient in whom it was slightly elevated. It is of considerable interest that the lipase content of the duodenal fluid in all patients who were tested was low and in one patient there was simultaneous lowering of the amylase content. It should be pointed out that the serum lipase

was determined on only one occasion in each of the patients and that the duodenal lipase levels refer to concentration on routine studies and not with the use of the secretin stimulation technic [16]. The values observed are lower than normal in our laboratory. The serum lipids were slightly elevated in two and normal in the

rest. The serum phospholipid levels were normal in all but one case. The serum cholesterol was slightly elevated in three instances but in the other cases was low. The free cholesterol fraction was somewhat low in three cases. Serum bilirubin levels were normal in all cases. There was no radiographic evidence of pancreatic calcification even in the patient with pancreatitis proved at operation.

COMMENTS

It would seem likely that infection and stasis had very little to do with the formation of gallstones in our patients.

Chemical alterations in the bile in relation to cholelithiasis have been studied very carefully by Isakkson [18,19,20,21]. Bile salts have properties similar to long-chain fatty acids in relation to their ability to cause dispersion of lipids such as cholesterol [22]. The work of Isakkson has shown that large amounts of lecithin are present in bile and that lecithin has a marked capacity to keep cholesterol in solution, in the form of a lecithin bile salt complex. From studies of the electrophoretic patterns of bile, it seems that this complex might include a lipoprotein when the bile is in the natural state [23]. The second important point is the presence of almost twice the normal amount of cholesterol in the pathologic as compared to normal bile [19]. The bile in our patients was not studied by this technic.

The most obvious systemic factor leading to the formation of gallstones is hemolytic anemia, with increased excretion of bile pigments and consequent formation of biliary stones [24]. There was no evidence that this was an important feature here.

Dietary studies in hamsters have shown that one can initiate the formation of gallstones on an almost fat-free and cholesterol-free diet. In these animals there is no evidence of increased turnover of cholesterol by the liver, suggesting other factors as a cause of stones [26,27,28]. Finally, one must mention the most recent work in which gallstones have been produced in rabbits by feeding them beta-cholestanol, a substance present in small amounts in the normal cholesterol fractions of the body [29]. These stones consist mostly of bile acids, differing in this respect from ordinary cholesterol and pigment stones.

Hypercholesterolemia has been noted in patients with cholelithiasis [2,4]. This has been assumed to mean that there is excessive biliary excretion and hence precipitation of cholesterol

in the bile when a critical concentration is reached. This may well be true in patients with essential hypercholesterolemia, although a thorough analysis of this point in such families apparently has not been made [25]. In our own patients, two had elevation of the serum cholesterol and four had a normal serum cholesterol. The two patients who had the most pertinent evidence for pancreatitis as the primary disease had low serum cholesterol levels whereas the patients who had suggestive evidence of cholelithiasis had hypercholesterolemia. We have left T. W. out of this discussion since we have good evidence that he was on a starvation diet both before and for a time after the serum cholesterol was determined. Several months later, when he had been repleted, the total serum lipid and cholesterol were somewhat elevated. At this time a T tube was present in the common duct.

The studies of hyperlipemia and its relation to gallstone formation are scanty [3,20]. Although some values in our patients were at the upper limit of normal, there were no markedly elevated levels and most of the values were well within normal limits. One of the high values was in a patient with cholelithiasis as the chief feature of his disease. His serum cholesterol and phospholipids were elevated, following the pattern noted in a recently studied group of patients with cholelithiasis [3]. Two of the patients with suggestive pancreatitis had normal values but T. W. had a value at the upper limit of normal several months after operation.

Elevation of the serum amylase and lipase is associated with acute pancreatitis. It is curious that all but one of these patients had an elevated blood lipase and a low duodenal lipase. The highest lipase value was in the patient with the highest lipid values. These figures must be interpreted with caution as they were not confirmed by repeated determinations and the duodenal drainage studies were carried out without secretin stimulation. Nevertheless, it will be of interest to compare these values with others obtained in patients with hyperlipemia and with other families with the syndrome described.

Hormonal factors in cholelithiasis have been described but were not investigated in this study [4].

It was noted earlier that the evidence for the familial form of pancreatitis [15] in this group of patients is not strong. One patient had pancreatic disease proved at operation. In the two other patients (F. W. and G. O.) the diagnosis is based on history. Both of these patients had

evidence of biliary tract disease. It is usually considered that biliary tract disease precedes pancreatic disease but this may not always be the case [14,15]. The possibility exists that in a certain group of patients biliary disease is a result of the factors responsible for pancreatic disease. It seems that this might be a more plausible explanation for the two patients cited. In these two patients the serum lipids studied were normal [27]. There seems to be no relation of hypercholesterolemia to pancreatitis in our patients.

SUMMARY

A family with an unusual incidence of cholelithiasis and possible associated pancreatitis was studied. The patients with cholelithiasis had an associated elevation in serum cholesterol and one of these had an increase in other components of the serum lipid fraction. The patients with pancreatitis had normal serum lipid levels.

Recent studies dealing with factors which appear to be important in the formation of gallstones are reviewed in relation to the patients presented.

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The Effect of 5-Hydroxytryptamine on Intestinal Motor Function in Man*

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SEROTONIN or 5-hydroxytryptamine (5-HT), also called enteramine, is believed to be produced by the argentaffin cells of the alimentary tract [1,2]. Most studies of this substance have been concerned with its action on the vascular and central nervous systems. Even Erspamer, who first obtained 5-HT from gastrointestinal mucosa, did not ascribe a physiologic role to 5-HT in gastrointestinal function [3]. On the other hand, more than fifty years ago, Ciaccio suggested that argentaffin cells secrete a substance similar to epinephrine [4]. Later Masson, on the basis of histologic studies, believed that these cells have a neuroendocrine function in the intestine [5,6]. As 5-HT production now is known to be increased in patients with metastasizing argentaffinomas [7,8], and since diarrhea is frequently a symptom of these tumors [9,10], Masson's suggestion seems more plausible than when it was first made. Since 5-HT also causes isolated intestinal strips to contract [3,11] and stimulates motor activity of Thiry-Vella loops in dogs [12], a study of the action of 5-HT on the intact intestine in man was undertaken.

METHODS

A double-lumen tube equipped with a balloon of 40 to 45 ml. capacity was passed into the upper jejunum under fluoroscopic observation, and intestinal motor activity was recorded by a balloon kymograph technic [13]. In this system the volume of the balloon is recorded, but the system is not completely isobaric. When all the air is displaced from the balloon the pressure in the system is 21.5 cm. water; when the balloon is filled to 45 ml. the pressure is 13 cm. water.

5-Hydroxytryptamine (serotonin creatinine sulfate)§ was given in single, quick, intravenous injections. Starting at 0.5 or 1.0 mg., the dose of 5-HT was increased in 0.5 mg. steps until an intestinal response was obtained or until a dose of 2.5 to 3.0 mg. was given. The interval between injections was at least fifteen minutes, or as much longer as necessary for intestinal motility to return to the control level. The onset and duration of subjective effects of the drug were timed by stop watch.

In some of the tests 5-HT was also introduced into the intestine adjacent to the recording balloon through the second lumen of the tube.

RESULTS AND COMMENTS

The Intestinal Response to Intravenous 5-HT. Thirty-seven balloon kymograph recordings of intestinal motor activity were made in thirty-four normal subjects. In thirty-one of these thirty-seven studies (84 per cent) intravenous 5-HT changed intestinal motor activity. The intestinal response to a given dose of 5-HT was reproducible and tachyphylaxis was not encountered.

Stimulatory action of 5-HT: In twenty-six tests (70 per cent), intestinal tone|| abruptly rose ten to sixty seconds (mean thirty-two seconds) after the injection of 5-HT and remained elevated for one to eight minutes (mean 3.7). During the period of increased intestinal tone only the rhythmic, 11 per minute,

§ Supplied by The Upjohn Company, Kalamazoo, Michigan.

|| Intestinal tone, as used in this paper, refers to the resistance of the intestine to distention. When intestinal tone is high, the pressure in the recording system produces little or no filling of the balloon; when intestinal tone is low, the balloon fills readily.

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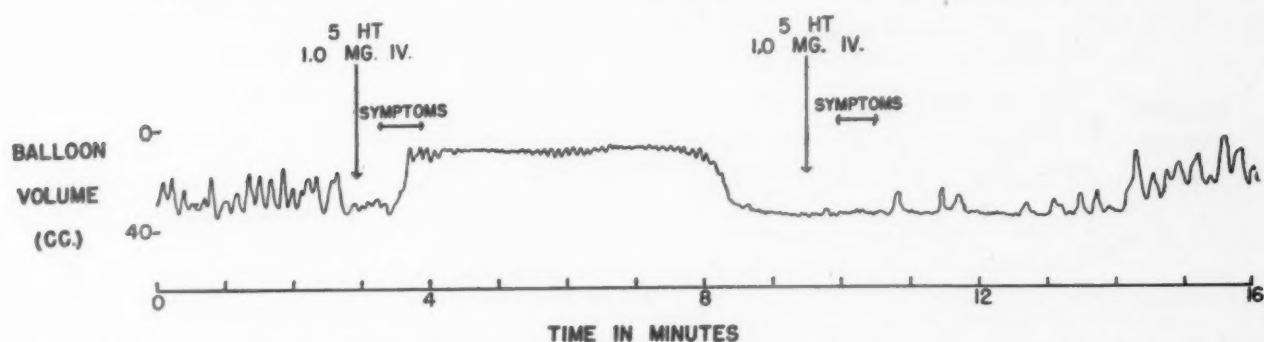


FIG. 1. Balloon kymograph record showing increased intestinal tone following 5-HT and insensitivity of intestine to 5-HT during the hypotonic period.

type I waves [14] were seen and these, too, were abolished when the increase in tone was maximal. (Fig. 1.) Following the contractile phase, intestinal tone often fell below the pre-injection level, and phasic activity was decreased or absent for one to six minutes and occasionally for as long as fifteen minutes. During this hypotonic period the intestine was insensitive to further 5-HT stimulation. In general, the more intense the contractile response, the longer and more complete was the subsequent period of inactivity. This inactive period may not be the specific result of 5-HT action, for similar depressed motor activity is seen after other intense and tonic intestinal contractions, such as those that may occur spontaneously [15] or after the administration of morphine [15,16].

Inhibitory action of 5-HT: In five studies in four individuals a totally different response to 5-HT was observed; injections of the agent were followed by a moderate decrease in tone and complete inhibition of phasic activity. (Fig. 2.) This inhibition lasted from one to three minutes; then normal phasic activity and tone returned. In these four subjects this was the only type of response noted; no response was seen with a smaller dose of 5-HT, and larger doses merely lengthened the period of inhibition.

The transient inhibition of tone and motility observed after the administration of 5-HT in these four subjects grossly resembled the intestinal motor responses recorded in animals given epinephrine intravenously [17]. For this reason the intestinal response to 5-HT and epinephrine were compared in these same subjects. Both caused similar inhibition of motility and thus suggested that 5-HT might act by way of the adrenergic nerves or by potentiation of epinephrine. (Fig. 2.) Phentolamine (regitine®), when given to three of these subjects, blocked the response to epinephrine without altering the

response to 5-HT. However, the failure of phentolamine to antagonize 5-HT does not completely exclude the possibility that 5-HT inhibition is mediated through adrenergic activity, for it has been shown that adrenergic blocking agents neutralize the effects of parenteral epinephrine more effectively than they antagonize the effect of adrenergic nerve stimulation [18].

Effect of Intraintestinal 5-HT. 5-HT was given into the jejunum above the recording balloon in twelve subjects who had responded to intravenous 5-HT. Intestinal motility was not altered nor were side effects noted in any of the subjects with doses of 5-HT ranging from 4 to 30 mg.

Side Effects of 5-HT. Immediately after intravenous injection, tingling or pain was frequently felt at the injection site or along the course of the injected vein, which went into intense spasm. Ten to thirty seconds (mean twenty-two seconds) after the injection, or about ten to fifteen seconds before the intestinal response, a prickling, burning sensation in the throat, tongue, lips and cheeks commonly occurred. This was often described as a feeling of warmth spreading from the lips to the face and over the neck and shoulders, although actual flushing was never present. Transient hyperpnea and tachypnea were frequently noted but only occasionally did the subjects complain of difficult breathing. All side effects disappeared within forty seconds.

None of the subjects experienced abdominal discomfort, cramps or rumbling, and none felt the urge to void or defecate.

The Mechanism of the Stimulatory Action of 5-HT on the Intestine. To investigate the site of action of 5-HT, the effects of several types of pharmacologic agents on the intestinal response to 5-HT were studied.

Histamine and antihistaminics: Feldberg and

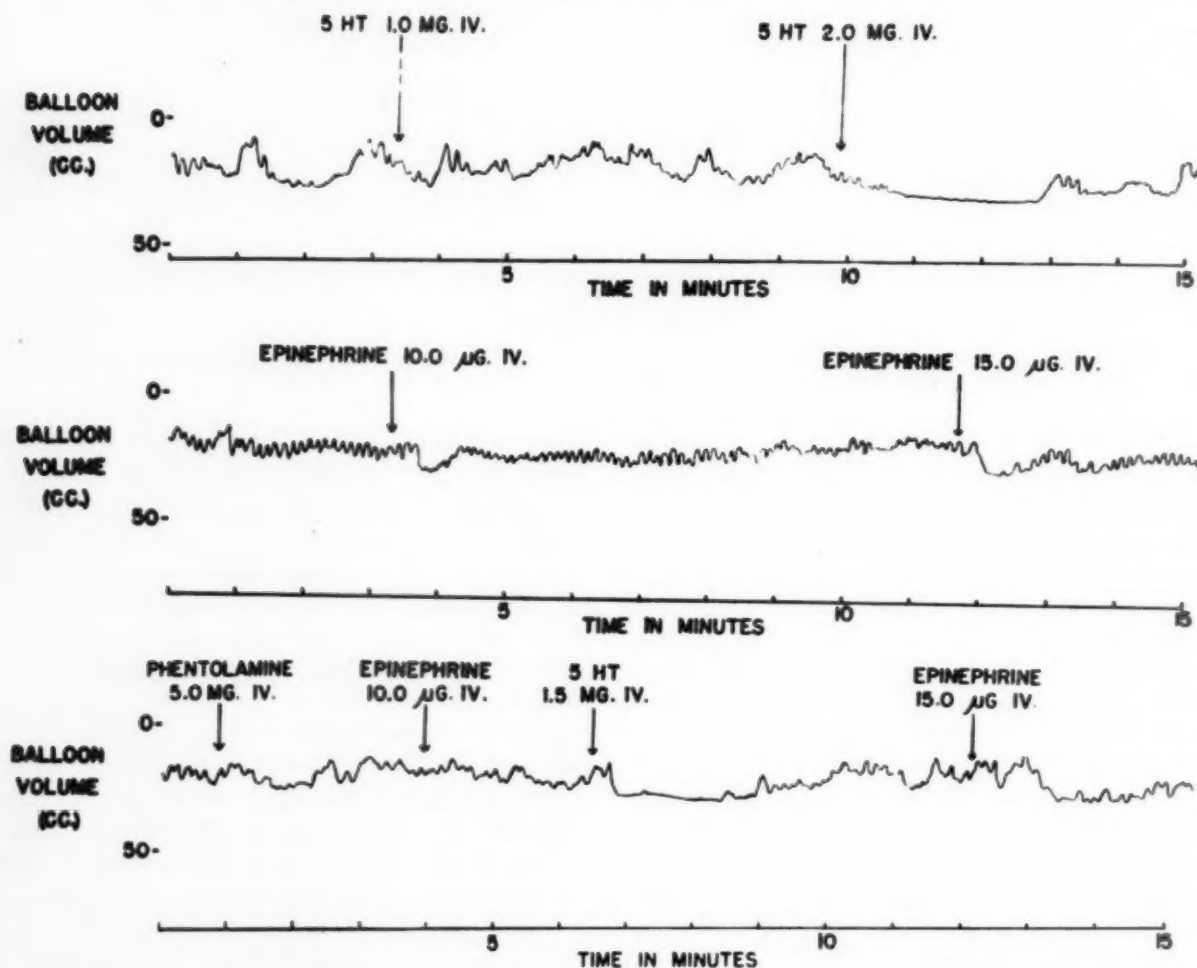


FIG. 2. Inhibition of intestinal motor activity by 2.0 mg. 5-HT and epinephrine is shown in the upper two tracings. In the lower tracing phentolamine blocked epinephrine without alerting the response to 5-HT.

Smith [19] described histamine release by 5-HT, and Page and McCubbin [20] concluded that histamine release mediated the fall in blood pressure in dogs and cats given 5-HT. Since histamine stimulates the intact dog duodenum [27] and the isolated guinea pig ileum [22] to contract, the possibility that 5-HT might act on the intestine by histamine release was tested as follows: (1) histamine and 5-HT were each given intravenously to five subjects and their intestinal effects compared; and (2) the effect of several antihistaminic drugs upon the intestinal response to 5-HT was determined.

Histamine was given in single injections of 0.03 to 0.05 mg. histamine base to four subjects; the fifth received an intravenous infusion of 0.025 mg. per minute for five minutes. Not one showed any alteration in intestinal motility despite prominent flushing and transient headache. Each subject easily distinguished the histamine side effects from those of 5-HT. With

histamine, objective as well as subjective flushing occurred; whereas 5-HT produced a prickling warmth but no visible flushing.

If the intestinal effect of 5-HT is in any way mediated by histamine, antihistaminics might be expected to diminish the response. In each of thirteen subjects, after the minimal dose of 5-HT capable of altering intestinal motility had been determined, an antihistaminic drug was given either intravenously or intraenterically and the responsiveness of the intestine to 5-HT was again determined. (Table 1.) In no instance did the antihistaminics abolish or even reduce the intestinal response to 5-HT. Indeed, in seven of nine subjects given intravenous antihistaminics, potentiation occurred, evidenced either by a prolongation of the tonic contraction produced by the effective dose of 5-HT, or by a response to a previously ineffective dose. (Fig. 3.) Although studies in dogs indicate that pyrilamine and tripeleennamine stimulate intes-

TABLE I

Subject	Drug	Dosage	Response
1	Pyrilamine maleate (neoantergan, anthisan)	25 mg. intravenously	Increased duration following 1.5 mg. 5-HT
2		25 mg. intravenously	Minimum effective dosage of 5-HT reduced from 1.5 to 1.0 mg.
3		25 mg. intravenously	Minimum effective dosage of 5-HT reduced from 2.0 to 1.5 mg. and response changed to depressor type
4	Diphenhydramine HCl (benadryl)	20 mg. intravenously	Increased duration following 1.5 mg. 5-HT
5		20 mg. intravenously	No change in 5-HT response (subject had depressor response throughout)
6		20 mg. intravenously	Minimum effective dose of 5-HT reduced from 1.5 to 1 mg.
7		20 mg. intravenously	Minimum effective dose of 5-HT reduced from 2.0 to 1.0 mg.
8		50 mg. into intestine	No change in 5-HT sensitivity
9	Tripelennamine HCl (pyribenzamine)	20 mg. intravenously	Increased duration following 1 mg. 5-HT
10	Chlorpheniramine maleate (chlortrimeton)	10 mg. intravenously	No change in 5-HT sensitivity (unresponsive to 5-HT).
11	Phenindamine tartrate (thephorin)	50 mg. into intestine	No change in 5-HT sensitivity (unresponsive to 5-HT)
12		50 mg. into intestine	No change in 5-HT sensitivity, but response converted to depressor
13		50 mg. into intestine	No change in 5-HT sensitivity (depressor response throughout)

tinal motility and that diphenhydramine inhibits motility [27], this direct action does not appear to be a factor in our studies, as these drugs by themselves caused little or no alteration in our balloon kymograph records.

The potentiation of the intestinal effect of 5-HT by intravenous antihistaminics noted in our subjects may be analogous to the potentiation of the pressor effect of epinephrine by antihistaminics described by Loew [23]. Both 5-HT and epinephrine are degraded by monoamine oxidase, an enzyme present in high concentration in the intestinal tract and acting on amines with the amino group attached to the terminal carbon atom [24]. Monoamine oxidase has been shown to be inhibited by many antihistaminic agents [25]; hence the potentiation of 5-HT by these drugs may well be due to interference with amine oxidase activity.

Experiments using isolated animal intestine indicate that after antihistaminics the response to 5-HT is unaltered [12,26] or inhibited [27]. The fact that these results differ from ours may have several explanations. When given intra-

venously a large proportion of 5-HT is degraded in its passage through the lungs and never reaches the gut. It was probably by inhibition of monoamine oxidase in the pulmonary vascular tree that antihistaminics exerted their major effect in potentiating the intestinal response to 5-HT in our subjects. In contrast, degradation of 5-HT by intestinal monoamine oxidase probably is not a limiting factor in the isolated intestine preparation and therefore it might be expected that the potentiating action would be less apparent.

Our studies do not suggest that histamine release is responsible for the effect of 5-HT on the human intestine, since this response was not duplicated by intravenous histamine and was not inhibited by any of the five antihistaminics.

Anticholinergic drugs: After intravenous injection of acetylcholine, balloon kymograph records from canine intestinal loops show increased intestinal tone followed by a period of hypomotility [28]. To determine whether or not the contractile response to 5-HT is mediated through the cholinergic nerve endings, the effect of the

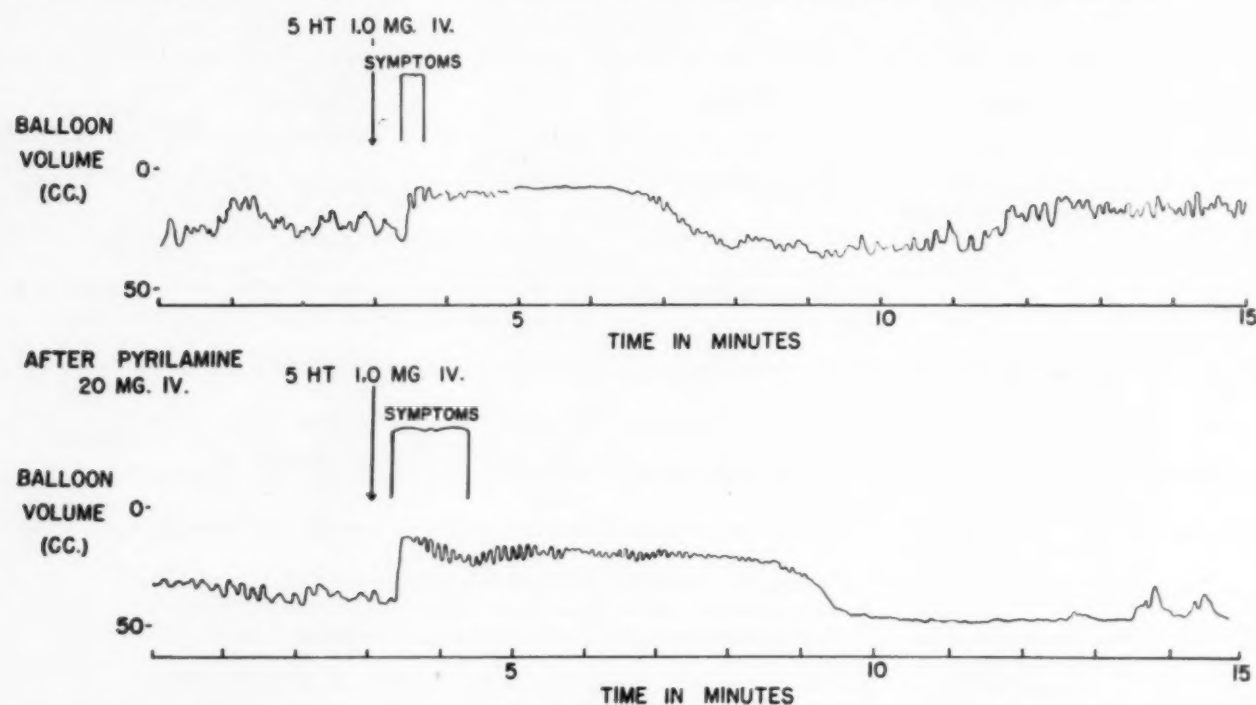


FIG. 3. Following pyrilamine, the duration of the tonic contraction induced by 5-HT is prolonged.

anticholinergic drugs methantheline (banthine®) and atropine on the intestinal response to 5-HT was tested. After the minimal effective dose of 5-HT was determined, methantheline, 50 mg. was given intravenously to three subjects, and two other subjects received atropine, 1.2 mg. intravenously. During the period of decreased

intestinal tone and phasic activity that follows these anticholinergic drugs the intestinal response to 5-HT was blocked. (Fig. 4.) It seems likely that this represents specific inhibition rather than diminished responsiveness of a non-specific nature associated with decreased intestinal motility and tone, since hexamethonium,

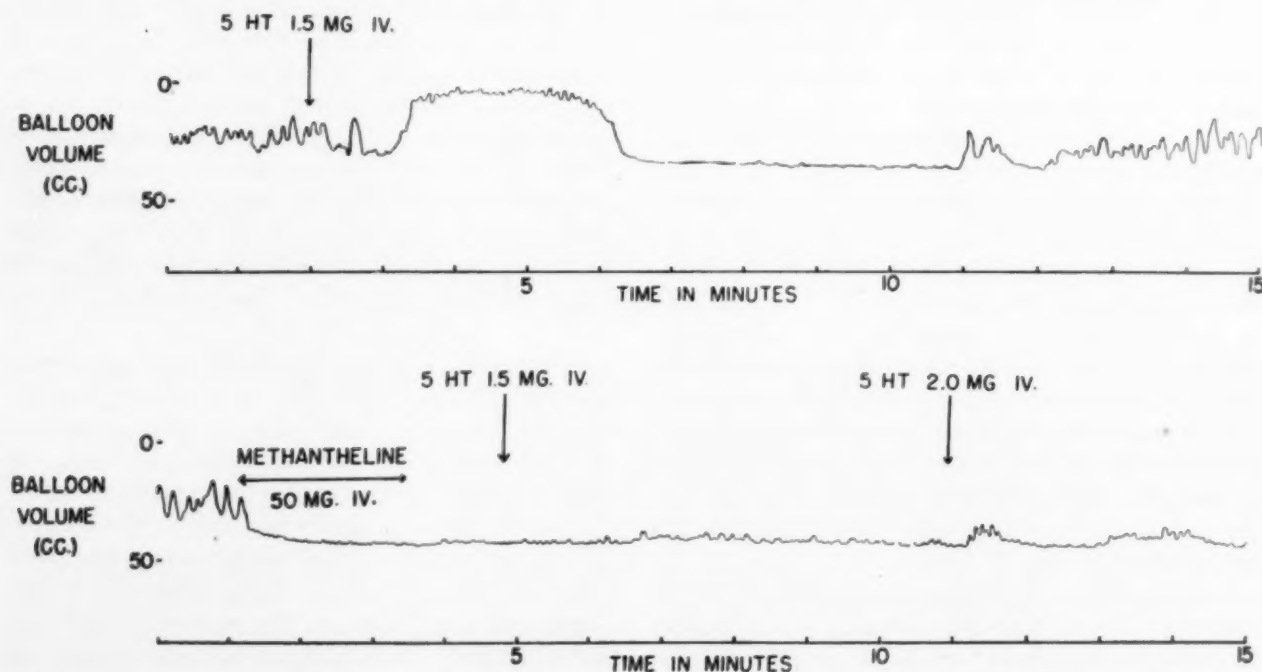


FIG. 4. The intestinal response to 1.5 mg. 5-HT, shown in the upper tracing, is completely blocked by methantheline (lower tracing).

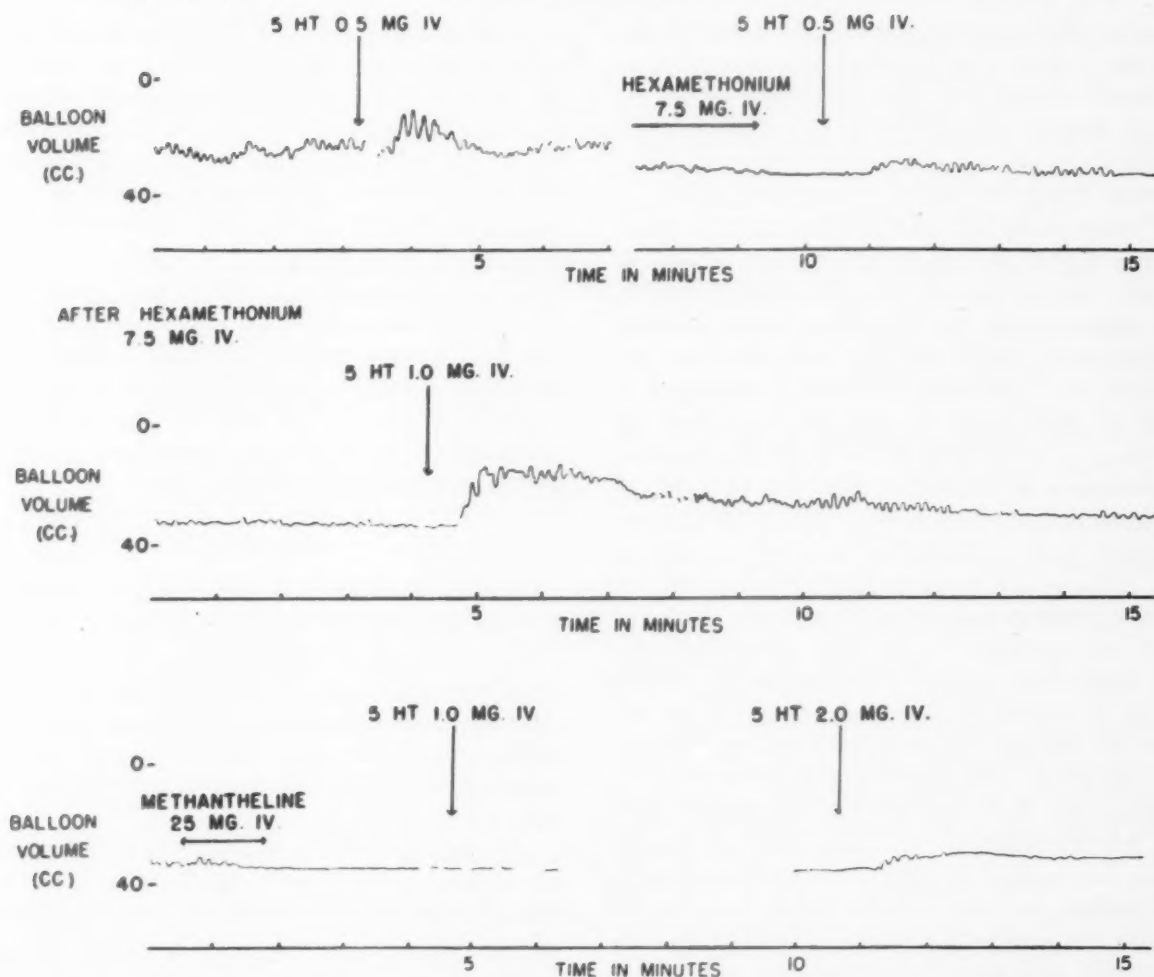


FIG. 5. These tracings from a single study show the failure of ganglionic blockade to inhibit the effect of 5-HT on the intestine. In the upper tracing a minimal response to 5-HT is shown before and after hexamethonium. In the second tracing, a continuation of the first, 1.0 mg. 5-HT increased intestinal tone appreciably, in spite of decreased tone resulting from ganglionic blockade. The effectiveness of methantheline in blocking the response to 5-HT is shown in the bottom tracing.

as will be described subsequently, also depressed intestinal tone but did not impair the intestinal response to 5-HT. It is possible, therefore, that 5-HT stimulates intestinal motility through parasympathetic pathways or by potentiating acetylcholine action. Further support for the view that 5-HT acts through acetylcholine release is provided by Robertson's observation that stimulation of the isolated rabbit ileum by 5-HT is potentiated when cholinesterase is inhibited [29]. Our observation that anticholinergic drugs block 5-HT is in agreement with the *in vitro* experiments of Rocha e Silva et al. [11] and Robertson [29] but at variance with those of Gaddum [22] and Feldberg and Toh [26].

Ganglionic blockade: The effect of ganglionic blockade with hexamethonium bromide was investigated next. Since methantheline has weak ganglionic blocking action, the tests with hexa-

methonium also served to determine whether or not any of the effect of methantheline could be ascribed to ganglionic blockade.

In two subjects the minimum effective dose of 5-HT was determined. With the subjects tilted in a 60 degree position, hexamethonium was given intravenously until hypotension was produced. After the subjects were returned to the horizontal position, responsiveness to 5-HT was determined again. In neither subject was the response to 5-HT abolished, although methantheline given subsequently blocked the intestinal effect of 5-HT. (Fig. 5.) These findings suggest that the inhibition of 5-HT by methantheline is not explained by ganglionic blockade, and suggest, as do the *in vitro* studies of Rocha e Silva [11] and Gaddum [30], that 5-HT alters intestinal motility at a site distal to the ganglionic synapse.

5-hydroxytryptamine analog: In four subjects the intestinal response to 5-HT was recorded before and after intravenous administration of 75 to 100 mg. BAS (1 benzyl-2, 5 dimethylserotonin), a benzyl analog of serotonin which has been shown to block the blood pressure response to 5-HT in animals [37] and in man [32]. In three subjects 5-HT by itself stimulated intestinal motility, and in one subject it produced inhibition. Both types of responses were greatly diminished by BAS and in two subjects the response was completely blocked. Inhibition of 5-HT by BAS was incompletely reversed by increasing the dose of 5-HT. BAS also diminished the symptoms which follow injection of 5-HT.

Transmission of excitation along the neuromuscular pathway can be blocked at several sites, such as the muscle itself, the myoneural junction, the postganglionic neurone and the ganglionic synapse. Since BAS alone did not alter intestinal motility, its blocking action cannot be explained by a direct effect on the intestinal muscle cell. As BAS blocked both the stimulatory and inhibitory effects of 5-HT, it is unlikely that BAS acts at the myoneural junction, for stimulation and inhibition of the intestine are caused by different chemical mediators. Indication that 5-HT does not act at the ganglia has already been presented. By the process of exclusion it is therefore possible to infer that BAS inhibits the effects of 5-HT on the intestine by competing for a specific receptor site on the postganglionic neurone. Evidence for specific receptor sites for 5-HT on the postganglionic neurone is provided by the observations of Gaddum [22] and Rocha e Silva [17] that stimulation of the isolated gut by 5-HT can be blocked without altering the responsiveness of the preparation to acetylcholine, histamine or nicotine. Also, Rocha e Silva showed that cocaine, which is believed to block transmission through nerve fibers, inhibits the stimulating action of 5-HT on isolated gut [17].

COMMENTS

Our findings indicate that 5-HT usually increases tone in the intact human small intestine, as it does in the isolated intestine of animals, but occasionally tone is decreased. This contrary effect is unexplained, unless 5-HT, like nicotine [33], stimulates both cholinergic and adrenergic postganglionic nerves. If so, it is possible that the adrenergic effect predominates in some individuals.

As little as 1 mg. 5-HT administered intravenously had a pronounced effect on intestinal motility in 25 per cent of our normal subjects. Since as much as two-thirds of the circulating 5-HT may be degraded in a single passage through the pulmonary vascular bed [34], the amount of 5-HT reaching the intestine is quite small, but nevertheless it is probably greater than is ever present under physiologic conditions. Therefore, our studies do not prove that 5-HT has any physiologic function with respect to the intestine but they suggest, as does the histologic evidence of Masson [6], that the argentaffin cells and 5-HT may affect the motor activity of the intestine under certain conditions.

SUMMARY

The effect of 5-hydroxytryptamine (serotonin) on intestinal motility has been investigated by means of balloon kymography in thirty-seven studies in thirty-four healthy persons. In twenty-six studies intravenous injection of 5-HT was followed by increased intestinal tone, in five it was followed by decreased tone, and in 6 no effect was noted.

The intestinal response to 5-HT was affected by drugs as follows: (1) potentiated by antihistaminics; (2) inhibited by a benzyl analog of serotonin; (3) inhibited by anticholinergic drugs (methantheline and atropine); and (4) unaltered by ganglionic blockade by hexamethonium.

The available pharmacologic evidence suggests that 5-HT stimulates intestinal motor activity through cholinergic nerves at a site distal to the ganglionic synapse.

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Confirmation of Achylia by Radioactive B₁₂ Uptake and Blood Pepsin Measurement*

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IN 1952 it was shown that intrinsic factor activity could be gauged indirectly by measuring the fecal excretion of a known dose of radioactive cobalt-labelled vitamin B₁₂ [1]. Subsequently, this procedure was modified by measuring the excretion of radioactive cobalt in the urine as an index of prior intestinal absorption [2]. A third way of detecting intrinsic factor activity is by measurement of radioactivity over the liver after the ingestion of radioactive vitamin B₁₂ [3]. The urinary method has been the simplest so that it has been widely used.

Intrinsic factor has no known stimulus, and the level of intrinsic factor activity apparently does not change over a short period of time. In this it is similar to blood pepsin activity, which also probably reflects the unstimulated activity of the stomach. For this reason it seemed worthwhile to ascertain whether or not intrinsic factor activity and the blood pepsin level might show any relation and whether or not failure of intrinsic factor function, as well as the presence of achylia, might be predicted by blood pepsin activity. Intrinsic factor activity may be related to the secretions of the mucous neck cells of the fundus, while pepsin comes from the chief cells. There is no reason, therefore, to expect these different cells always to have parallel activity, but the failure of the stomach to secrete acid while pepsin and intrinsic factor activity persist made the relationship appear plausible.

METHOD

Intrinsic factor activity was determined by the Schilling method [2] with certain modifications. No restriction of food or drink was imposed. Each patient received orally 0.5 µg. of radioactive vitamin B₁₂‡

‡ Supplied through the courtesy of Dr. Charles Rosenblum, Merck & Co., Inc., Rahway, N. J.

* From The Department of Medicine, Yale University School of Medicine, New Haven, Connecticut. This study was supported in part by grants from the U. S. Public Health Service (C-2578-physio), the Fluid Research Funds of Yale University, and the United Stamford Fund.

† Dr. Poliner was a Dazian Foundation Fellow during the period of this study.

having 0.06 microcuries of radioactivity. Two hours later 1,000 µg. of non-radioactive vitamin B₁₂ were

TABLE I

Patient	Diagnosis	Pepsin (units)	B ₁₂ Excretion in 24 Hours (%)
F. R.	Syphilitic aortitis and heart disease	800	16.1
A. C.	Acute rheumatic fever	265	14.8
F. J.	Normal male	290	38.2
H. B.	Infectious hepatitis	560	13
S. T.	Fever of unknown origin-? TBC	210	8.9
R. S.	Normal female	800	26.7
C. W.	Chronic gastritis	800	30.6
T. W.	Diabetes	430	9.3
A. P.	Normal female	380	15.5
J. D.	Normal female	245	12.7
L. G.	(1) Carcinoma of the stomach (2) Diabetes mellitus	275	12.3
E. S.	(1) Lymphosarcoma of the stomach (2) Diabetes mellitus	680	6
F. M.	Post total gastrectomy	65	1
J. P.	Pernicious anemia	265	0
M. B.	Pernicious anemia	220	1
R. H.	Pernicious anemia with subacute combined sclerosis	145	1.9
E. H.	Pernicious anemia	190	1.6
P. F.	Duodenal ulcer	480	15
E. M.	Gastric ulcer	750	9.7
M. D.	Gastric ulcer	400	17.9
M. S.	Marginal ulcer, post subtotal gastrectomy	280	10.8
W. S.	Post subtotal gastrectomy	225	14.4
W. C.	Post one-third subtotal gastrectomy	405	14.4
R. B.	(1) Subtotal gastrectomy (2) Chronic pancreatitis	260	14
M. F.	Post subtotal gastrectomy	310	8.3
E. H.	Achlorhydria	400	15
J. D. (VA)	Achlorhydria	215	13
B. C.	Achlorhydria	220	2.3
F. F.	Diabetes mellitus	385	12.4
R. W.	Achlorhydria	130	10.8
O. B.	Sprue	180	6.6
G. G.	Sprue	260	7.7
M. C.	Adrenal insufficiency	395	4.8
H. J. (VA)	Lymphosarcoma of small bowel with steatorrhea	430	1.97
A. R.	Severe regional enteritis	360	15.5
N. D.	Scleroderma	445	19.3
E. B.	Normal female	160	12.4

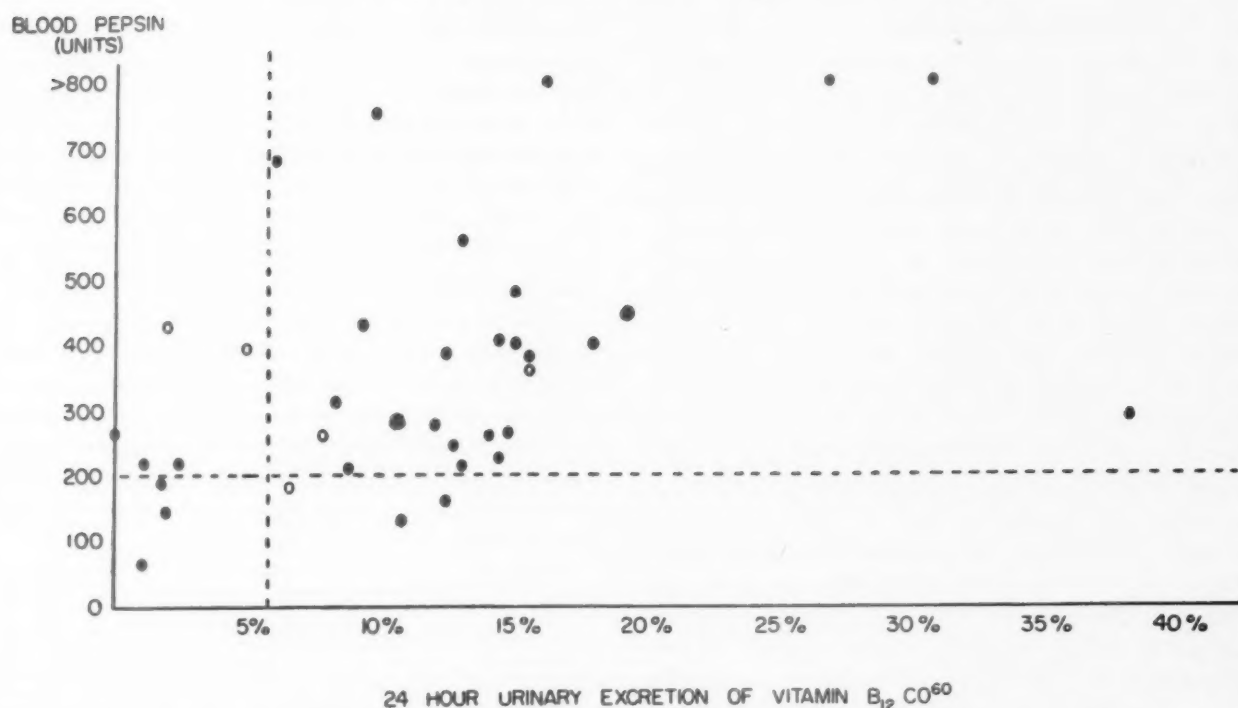


FIG. 1. Correlation of vitamin B₁₂Co⁶⁰ excretion with blood pepsin units in thirty-seven patients. O denotes patients with small bowel absorptive defects.

given parenterally. Urine was collected for twenty-four hours after the oral dose. No urine was accepted if there was any possibility of stool contamination. A 500 cc. or 800 cc. sample of urine was counted over a lead-shielded scintillation counter. Known amounts of the same sample of radioactive vitamin B₁₂ in the same volume of distilled water were also counted and calculated to bracket the unknown within 2 per cent of the unknown sample. The background activity was similarly determined, using an equal volume of distilled water, before and after each urine and standard sample. All unknown samples, background and standard samples, were counted for ten one-minute periods, and the average of these ten periods was used. Such counting periods rarely varied more than ± 10 per cent of the average. Thus the per cent of the original dose excreted in twenty-four hours could be calculated. The division between a normal and a low test was considered to be 6 per cent. This is higher than the level suggested by Schilling [2] but approximately the same as that found by MacLean [5]. Various methods have been suggested to reduce the error in counting, calculated at ± 10 per cent to ± 1 per cent. In view of the inherent biologic variations between patients we did not consider it any more accurate to obtain a lower per cent variation in our counting technic.

The blood pepsin level was determined by a modification of the Mirsky method as previously reported [4]. All determinations were made in duplicate. The majority of normal subjects exhibited values between 200 and 450 units.

RESULTS

Urinary radioactive B₁₂ excretion and blood pepsin levels were studied in thirty-seven patients. These results and the diagnoses of the patients are listed in Table 1, and charted in Figure 1.

There appears to be a close relationship between radioactive vitamin B₁₂ excretion and blood pepsin level only in the normal or higher range. Seven patients with a blood pepsin level over 450 units had normal radioactive B₁₂ excretion. Nineteen patients with blood pepsin levels in the normal range (200 to 450 units) had a normal radioactive B₁₂ uptake. Two patients with absorptive defects of the small bowel (lymphosarcoma of the small bowel and adrenal insufficiency) without any apparent gastric disease were studied. They had normal blood pepsin levels but showed the expected abnormally low radioactive B₁₂ excretion because of poor absorption. Two other patients with pernicious anemia and blood pepsin levels of 220 units and 265 units, respectively, had abnormally low vitamin B₁₂ uptakes. One patient, studied because of achlorhydria, had a blood pepsin level of 220 units and a B₁₂ uptake of only 2.3 per cent, but no anemia. Of six patients with low blood pepsin levels three had a low radioactive B₁₂ excretion, three had a normal excretion.

COMMENTS

It should be recognized that the radioactive B₁₂ urinary excretion test is an indirect measure of intrinsic factor activity. Vitamin B₁₂ must combine with intrinsic factor, must pass into the small bowel, must be absorbed, and then must be excreted. Finally, the measurement is not of intrinsic factor itself but of radioactive vitamin B₁₂ which has been absorbed and excreted after combination with intrinsic factor. The blood pepsin level indicates acid proteolytic activity in the blood, most of which certainly is of gastric origin. It is therefore unwarranted to attempt a direct quantitative correlation between intrinsic factor activity and blood pepsin activity. We are comparing a qualitative test (urinary excretion of radioactive B₁₂) with a semiquantitative test (blood pepsin). It is not surprising, therefore, to find that the patient with the highest value of radioactive B₁₂ excretion had a normal blood pepsin level. The urinary radioactive B₁₂ excretion is usually in the same range in patients with a high blood pepsin level as in those with a normal blood pepsin level.

The two patients with absorptive defects of the small bowel had a low radioactive B₁₂ excretion, but normal blood pepsin levels. The defect is presumably in small bowel absorption and not in lack of intrinsic factor, although the presence of intrinsic factor in the gastrointestinal tract was not proved. Interestingly enough, two patients with sprue had a borderline radioactive B₁₂ excretion.

A normal B₁₂ uptake was found uniformly in patients with high blood pepsin levels (above 350 units). As we have noted earlier, such patients do not necessarily have a higher radioactive B₁₂ excretion than subjects with normal blood pepsin levels in the lower range.

Patients with proved pernicious anemia have low radioactive B₁₂ excretion, and ordinarily a low blood pepsin (under 200 units) [4]. The patients with an abnormally low radioactive B₁₂ uptake and with a blood pepsin level lower than 200 units may be considered to have conditions in the stomach characteristic of pernicious anemia. In our experience, however, rare patients with pernicious anemia have low normal blood pepsin values. One patient, J. P., with a blood pepsin level of 265 units and a pH following histamine in the gastric juice of 5.7, appeared to have true pernicious anemia; since it was not possible to repeat these studies, however, the results remain only suggestive.

Another patient, B. C., with no detectable hematologic abnormalities had a radioactive B₁₂ excretion of 2.3 per cent in twenty-four hours and a blood pepsin level of 220 units. There was no detectable acid activity in the stomach secretions one hour after the administration of 0.5 mg. of histamine base. In this patient the low radioactive B₁₂ excretion of 2.3 per cent, the complete absence of gastric acid and the borderline blood pepsin are consistent with pernicious anemia, but no anemia was present. This is not surprising since it may take three to eight years to deplete the body's store of B₁₂ before anemia develops. It may be expected that if this patient survives long enough and if he receives no supplementary B₁₂ or folic acid, pernicious anemia will develop.

Findings in two other patients also emphasize transition stages in the development of complete achylia. E. B. was a seventy-four year old woman with no hematologic abnormalities who showed a radioactive B₁₂ uptake of 12.4 per cent and blood pepsin level of 160 units. A gastric analysis, however, showed a drop from a pH of 7.2 to a low of 3.3 sixty minutes after injection of 0.5 mg. of histamine base. R. W., a sixty-four year old woman, had a radioactive B₁₂ uptake of 10.8 per cent with a blood pepsin level of 130 units. Gastric analysis showed a fasting pH of 7.3 which became 6.9 after injection of 0.5 mg. of histamine base.

It may be expected that in patients with a normal radioactive B₁₂ uptake, a very low or absent gastric acid, and low blood pepsin levels a deficiency of intrinsic factor may also develop in the future if the process is one of progressive atrophy. An atrophic process should gradually affect all cells of the mucosa and their secretions at different times and to different degrees. It would appear that acid usually is the first secretion to disappear, then pepsin, and finally intrinsic factor activity. Other variations, however, may well occur. In adults, there is only one well documented case of absent intrinsic factor in the presence of gastric acid [7]; unfortunately, no pepsin studies were made in this patient. In children, however, there appear to be six proved cases of absence of intrinsic factor in the presence of gastric acid [8-12]. Gastric pepsin was studied in two of these children and found to be present in "normal amounts."

Atrophic gastritis may progress to give low blood pepsin and low gastric pepsin levels, yet there may be a normal radioactive B₁₂ excretion.

Presumably, in such patients pernicious anemia is developing and these patients form an intermediate group between achlorhydria and achylia.

Although a direct quantitative correlation between radioactive vitamin B₁₂ uptake and the blood pepsin level was not always found, in view of the probable sequence with which the various factors disappear from gastric secretion it seems safe to assume that intrinsic factor will be present in any patient with a blood pepsin value higher than 350 units. The converse is not always true; patients with a normal radioactive B₁₂ uptake may have a low blood pepsin level.

SUMMARY

The unstimulated phase of gastric secretion was studied by comparing the twenty-four-hour urinary radioactive B₁₂ test (of Schilling) and the blood pepsin level in thirty-seven patients. Many gradations and variations between normal gastric secretion (adequate intrinsic factor and gastric acid with normal blood pepsin level) to complete gastric atrophy (absent intrinsic factor and gastric acid with low blood pepsin levels) were found. Factors involved in these variations are discussed.

In general, a normal urinary radioactive vitamin B₁₂ excretion will be found in patients with a blood pepsin level above 350 units, but the converse is not always true.

Acknowledgment: The authors wish to express their appreciation to Dr. Arnold Welch and Dr. William Prusoff of the Department of Pharmacology, Yale University School of Medi-

cine, for their advice and assistance during the course of this investigation.

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The Effects of Corn Oil on Serum Lipids in Normal Active Subjects*

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LOWERING of the various serum lipid constituents by means of ingesting unsaturated oils has been clearly demonstrated in human subjects [1-14]. Most of these studies have been concerned chiefly with changes in cholesterol and beta lipoproteins. A number of oils of relatively high iodine number, namely: corn [7,9], cottonseed [2], soybean [6], sunflower seed, pilchard, seal [13], sesame oils [14], and unsalted nuts [3], have been shown to have distinct cholesterol-lowering properties. Beveridge [9] has given evidence that this effect of corn oil is greater than that of marked reduction in total fat intake alone. Changing a cholesterol-depressing oil by hydrogenation has produced rises in cholesterol [13].

Despite speculation [15,16] there is, as yet, no direct evidence that ingestion of unsaturated fats has any benefit in coronary artery disease. There is some reason to believe that a general reduction in daily fat intake increases the chances of survival following myocardial infarction [17]. Epidemiologic evidence has been gathered illustrating a decreased incidence of coronary artery disease in those populations manifesting low serum lipids. Apparently this is associated with low levels of lipid in the diet [18-29], although some hold a contrary opinion [30-32].

If it should be determined that the lipid-lowering effects of unsaturated oils are of benefit to patients with coronary atherosclerosis, it would be important to arrive at an effective practical regimen. The purpose of the present study was to observe the effects of a readily available unsaturated fat (corn oil, mazola® (Corn Products Refining Co.)) on a number of serum lipid constituents in healthy young men during periods of full activity utilizing diets known to be palatable and practical for long-term clinical use.

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EXPERIMENTAL

Subjects. Six healthy male medical interns between the ages of twenty-four and twenty-seven were selected. They carried on their full duties during the course of the study. Weights were recorded before the study and at weekly intervals thereafter in the postabsorptive state.

Diets. All meals were taken in the hospital dining halls under the supervision of the dietitians and us. During week 1 a control diet was given which was considered to be approximately the same as the customary diet of the subjects. This contained 2,940 calories, 100 gm. animal fat (31 per cent total calories), 402 gm. carbohydrate, 108 gm. protein. During week 2 and week 3 the diet contained the same number of calories but the composition was changed as follows: 30 gm. animal fat (9 per cent total calories), 70 gm. corn oil (22 per cent total calories), 418 gm. carbohydrate and 90 gm. protein. Thus 70 per cent of fat calories were provided by corn oil. The corn oil was emulsified in a blender at room temperature in about 500 cc. of fruit juice with some sugar and small amounts of lemon juice if desired (these calories included in total). It was taken directly in this form at intervals throughout the day. During week 4 and week 5 the initial 2,940 calorie, 100 gm. animal fat diet was reinstituted but the subjects continued to take the same quantity of corn oil prepared in the same way as in weeks 2 and 3. Thus they consumed 3,570 calories, 100 gm. animal fat (25 per cent of total and 59 per cent of fat calories) and 70 gm. corn oil (18 per cent of total and 41 per cent of fat calories), 402 gm. carbohydrate and 108 gm. protein per day during these weeks.

Lipid Studies. Blood was drawn weekly in the post-absorptive state and allowed to clot. Serum was separated and used for all the analyses. These analyses were performed in duplicate and the results of each duplicate determination averaged. In view of possible day-to-day variations in total cholesterol values, blood was drawn after three days on the "normal" control diet containing 100 gm. of animal fat per day, as well as after one week on this diet. The

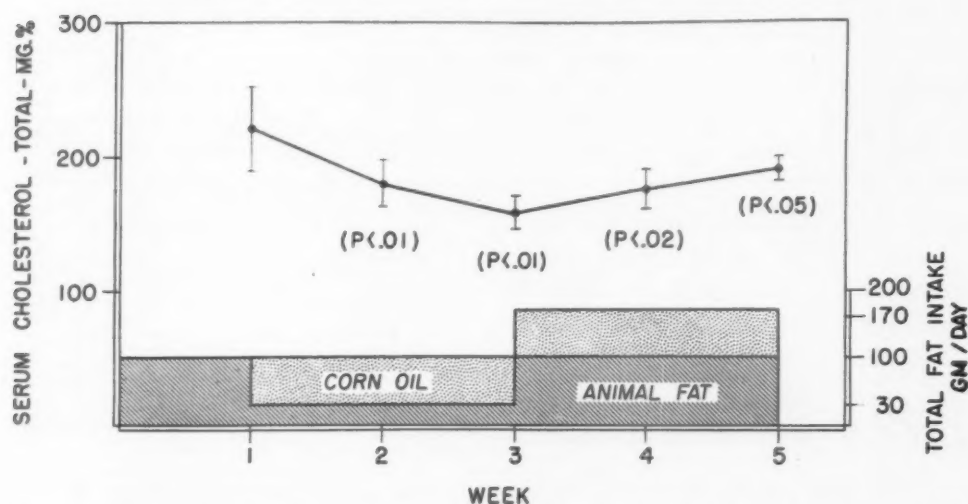


FIG. 1. Behavior and significance of mean values for serum total cholesterol on diets of differing fat composition.

control total cholesterol is an average of these two values.

Total cholesterol was obtained by the method of Pearson, Stern and McGavack [33]. The Sobel and Mayer modification of the Schoenheimer-Sperry method for free cholesterol was used [34]. Lipid phosphorus was determined by the method of Fiske and Subbarow [35]. Total lipid was obtained by gravimetric determinations on 3 cc. aliquots of serum after successive extractions by 3:1 alcohol-ether and petroleum ether based on Bloor's method [36]. Correction was not made for possible contamination by non-lipid nitrogenous materials as this was not believed to be significant in normal subjects [37]. Desiccation for at least sixteen hours before weighing was thought adequate to remove any residual water. Duplicate determinations generally agreed within 3 per cent. Iodine numbers were obtained by a standard method using Hanus' reagent [38]. So called "Allen lipid" was determined directly in millimeters using Allen tubes (E. Machlett & Son, New York) requiring 3 ml. serum according to the method of Allen [39]. Conversion of this value to mg. of fat per 100 ml. of serum, using the factor given by Allen, produced values which correlated poorly with determinations of lipid constituents by the gravimetric method. In control runs with olive oil 115 per cent recovery of fat was obtained, which was somewhat less than the 125 per cent recovery reported by Kibrick and Skupp [40]. In view of these results a correction was not made for this excess recovery, but instead the volume of fat, expressed as millimeters of height in the Allen tube, was used in following trends in total lipids. Duplicate runs of this test agreed quite closely. Lipoprotein patterns were obtained by electrophoresis on a Spinco Model R paper electrophoresis system. Percentage of color given by the beta fraction in relation to the total color was determined by staining the paper strips containing the separated fractions with oil red O,

cutting the strips, eluting and reading optical density of eluent according to the method of Jencks and Durrum [41].

The results of each analysis on the six individuals were averaged and the mean weekly values for each constituent were subjected to statistical analysis.

RESULTS

The diets were well tolerated, being compatible with a full work schedule. The fare did not appear dull; the corn oil emulsion was taken as a reasonably pleasant thirst-quencher. Weights varied insignificantly and no untoward symptoms developed.

Free and Total Cholesterol. (Table 1.) On the 30 gm. animal fat, 70 gm. corn oil diet, containing the same caloric composition as the control diet, there was a sharp drop in both free and total cholesterol by the end of week 1, and an even sharper drop by the end of week 2. (Figs. 1 and 2.) The mean total cholesterol dropped from a control value of 222 mg. per cent to 180.7 mg. per cent ($p < .01$) after week 1, and to 158.0 mg. per cent ($p < .01$) after week 2. When the total fat ingestion was increased to 170 gm. per day (100 gm. animal fat—25 per cent of total calories, and 70 gm. of corn oil—18 per cent of total calories) with an increase in caloric intake from 2,940 to 3,570 calories per day, there was a drift toward the control in both free and total cholesterol values. After week 4 the mean total cholesterol was 176 mg. per cent ($p < .02$) and at the end of week 5 it was 190.7 mg. per cent ($p < .05$).

Free cholesterol appeared more labile than total cholesterol, dropping to a greater degree,

TABLE I
SERUM LIPID FINDINGS

Subject	Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid P (mg. %)	Beta Lipoprotein (%)	Total Lipid (mg. %)	Allen Tube (mm.)	Iodine No.
<i>End of Control Week (100 gm. animal fat, 2,940 Calories)</i>							
1	228	70.7	8.53	74.7	834	30.1	68.6
2	267	77.2	10.07	74.1	864	29.2	70.2
3	202	65.4	7.80	65.0	717	22.2	72.9
4	184	54.9	7.44	72.5	645	21.4	72.4
5	244	75.6	8.50	79.5	777	26.5	75.0
6	207	63.5	7.76	74.1	725	21.3	71.5
Mean	222*	67.8	8.35	73.3	760	25.1	71.8
S. D.	±30.4	±8.35	±.95	±4.72	±81.1	±4.01	±2.2
<i>End of Second Week (30 gm. animal fat plus 70 gm. corn oil, 2,930 calories)</i>							
1	195	55.8	8.40	76.6	870	30.7	78.0
2	183	53.1	8.50	70.2	739	22.0	73.8
3	177	47.4	7.62	62.5	708	18.7	68.3
4	154	42.0	8.03	71.8	729	23.8	80.7
5	208	56.3	7.09	73.8	639	20.5	76.3
6	167	33.6	7.61	71.0	629	19.9	82.3
Mean	180.7	48.03	7.88	70.98	719	22.6	76.6
S. D.	±19.3	±8.94	±.54	±4.75	±87.1	±4.34	±5.1
P.	<.01	<.01	<.3	<.1	<.4	<.2	<.2
<i>End of Third Week (30 gm. animal fat plus 70 gm. corn oil, 2,930 calories)</i>							
1	160	38.8	7.70	72.9	760	21.2	72.9
2	170	40.9	8.55	71.7	713	23.0	76.4
3	167	44.3	8.07	64.0	643	18.7	75.2
4	149	24.9	7.18	65.2	582	16.2	76.1
5	167	35.7	6.97	71.7	604	17.5	75.1
6	135	25.5	6.99	65.5	569	16.5	74.8
Mean	158.0	35.01	7.58	68.5	645	18.9	75.1
S. D.	±13.6	±2.56	±.64	±4.00	±76.5	±2.73	±1.2
P.	<.01	<.01	<.05	<.02	<.01	<.01	<.02
<i>End of Fourth Week (100 gm. animal fat plus 70 gm. corn oil, 3,570 calories)</i>							
1	183	52.2	7.11	73.4	629	20.5	81.5
2	167	48.0	7.11	69.7	573	17.0	69.7
3	181	49.5	8.08	60.7	659	18.0	77.1
4	174	43.0	7.55	66.7	623	18.0	84.4
5	200	49.0	7.13	72.9	664	20.8	79.7
6	151	33.5	7.08	64.2	550	15.8	73.2
Mean	176.0	45.87	7.34	67.9	616	18.4	77.6
S. D.	±16.5	±6.76	±.40	±5.01	±56.9	±1.96	±5.4
P.	<.02	<.01	<.1	<.01	<.01	<.01	<.05
<i>End of Fifth Week (100 gm. animal fat plus 70 gm. corn oil, 3,570 calories)</i>							
1	197	54.4	8.65	72.8	770	26.0	82.0
2	182	50.2	8.45	73.3	822	29.5	76.8
3	189	50.2	8.97	60.8	669	20.0	72.8
4	183	46.8	7.96	61.0	590	17.8	73.7
5	205	51.8	7.62	72.1	620	21.0	79.6
6	188	45.9	7.74	66.4	590	21.0	80.2
Mean	190.7	49.88	8.23	67.7	677	22.6	77.5
S. D.	±7.92	±3.15	±.54	±5.85	±98.1	±4.34	±3.7
P.	<.05	<.01	<.2	<.02	<.01	<.05	<.05

* These values represent means of determination made at the end of three and seven days of the control period (see text).

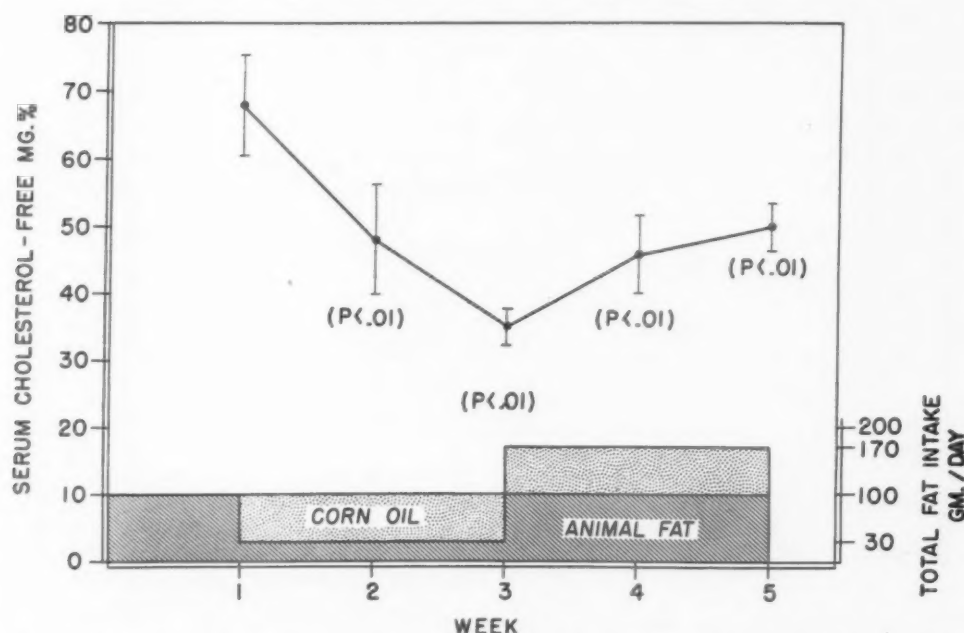


FIG. 2. Behavior and significance of mean values for serum free cholesterol on diets of differing fat composition.

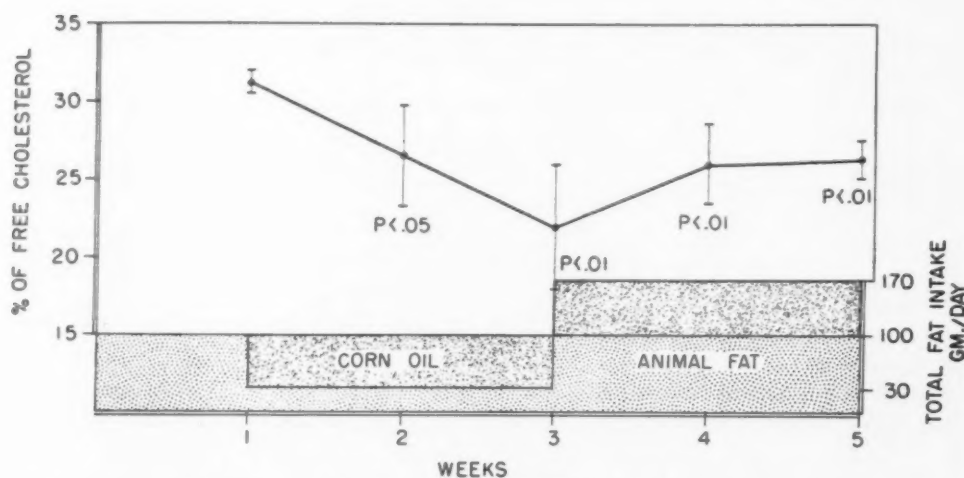


FIG. 3. Changes in mean values for per cent free cholesterol during observation period.

thus producing significant decreases in the percentage of free cholesterol (Fig. 3). The depression in free cholesterol, although drifting back toward the control value after the increased animal fat and caloric intake in weeks 4 and 5, remained significantly depressed (at the 1 per cent level of significance) throughout the period of corn oil ingestion.

Lipid Phosphorus (Table 1, Fig. 4). Lipid phosphorus changed to a smaller degree and more gradually than free and total cholesterol. The initial mean of 8.35 mg. per cent was 7.88 mg. per cent at the end of week 2 ($p < .3$), becoming significant at 7.58 mg. per cent

($p < .05$) at the end of week 3, but was 7.34 mg. per cent ($p < .1$) at the end of week 4, rising to 8.23 mg. per cent ($p < .2$) at the end of week 5. Thus in the course of this study lipid phosphorus changed only slightly, the only significant depression being reached at the end of week 3.

Total Lipid (Table 1, Fig. 5). Changes in total lipid were quite significant but developed more slowly than the changes in free and total cholesterol. The initial mean of 760 mg. per cent was 719 mg. per cent at end of week 2 ($p < .4$), 645 mg. per cent ($p < .01$) at end of week 3, 616 mg. per cent ($p < .01$) at the end of

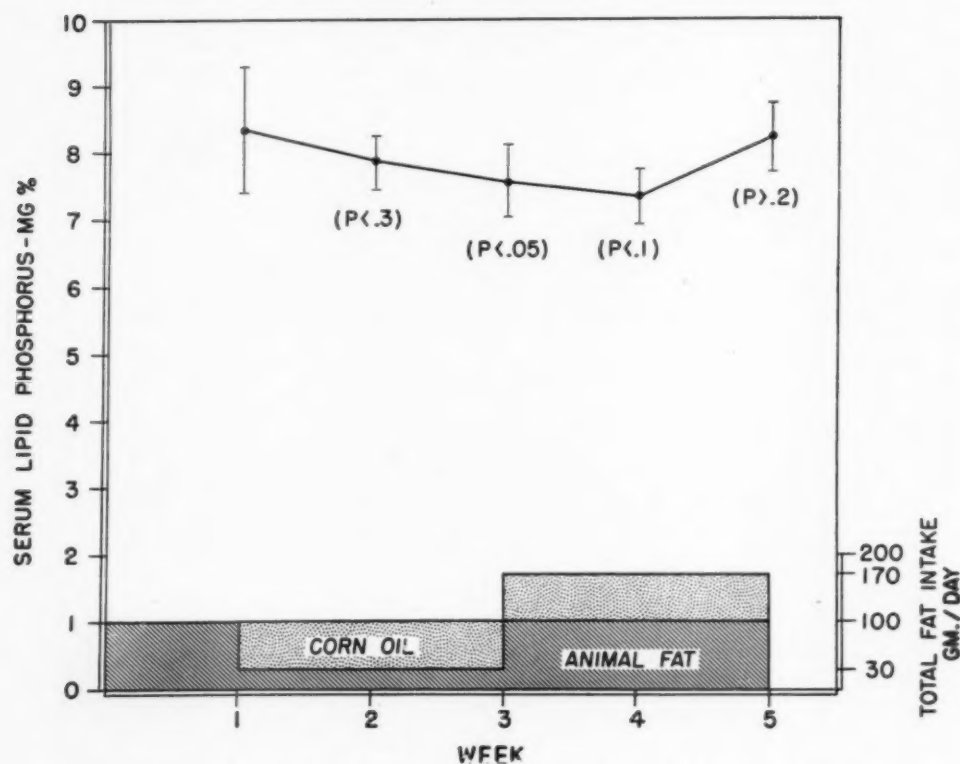


FIG. 4. Behavior and significance of mean values for lipid phosphorus.

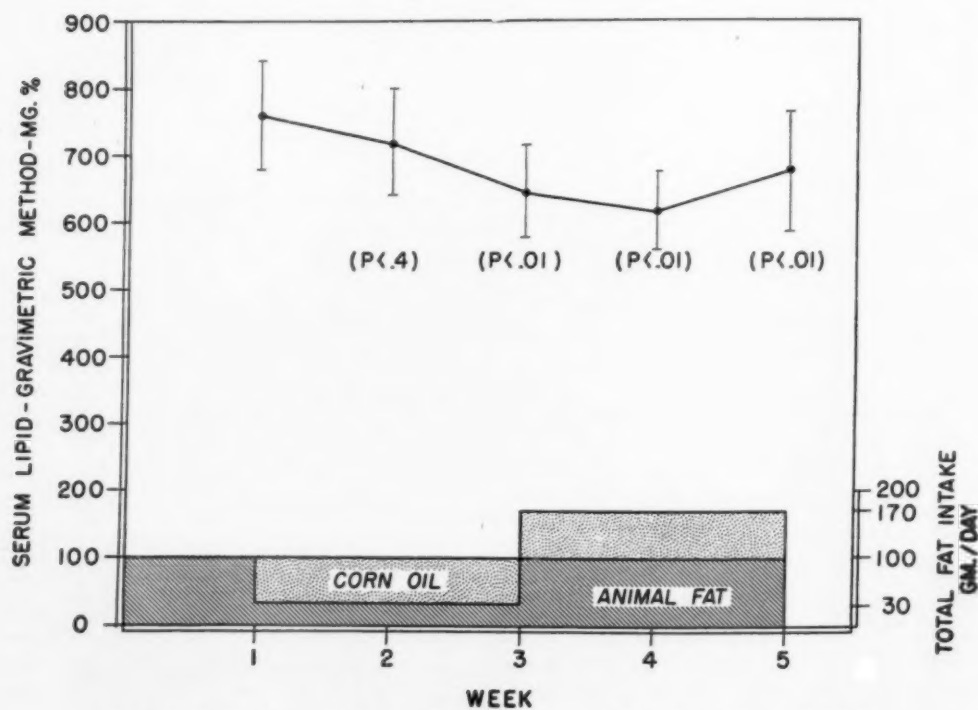


FIG. 5. Behavior and significance of mean weekly values for total lipid.

week 4 and 677 mg. per cent ($p < .01$) at the end of week 5.

The change in total lipid reached the 1 per cent level of significance at the end of week 3, or after two weeks on a 30 gm. animal fat, 70 gm. corn oil regimen. There was a still further depression

after one week of increased fat and caloric intake, week 4, but an upward drift after the second such week, week 5. Thus the change in total lipid seemed to lag about one week behind the changes in free and total cholesterol.

In order to get additional information about

the behavior of other fats, the values for total cholesterol and phospholipid (lipid P \times 25) were subtracted from the total lipid figure. (Fig. 6.) This value represents the neutral fats and the cholesterol ester fatty acids, and has been termed "residual fat." The variation in this value among

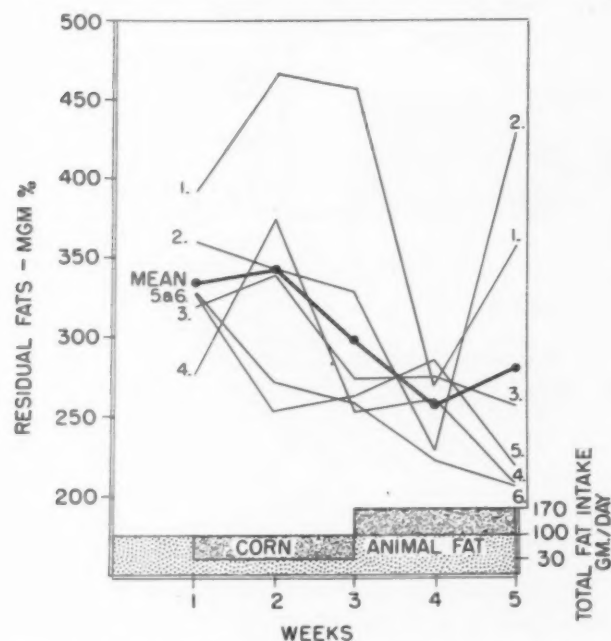


FIG. 6. Mean and individual values for residual fats (neutral fats plus cholesterol ester fatty acids).

the six subjects was marked during the first three weeks, but at the end of week 4 there was a definite depression over the previous weeks with a relatively narrow spread. By the end of week 5 the mean was lower than control, but the spread was again wide.

Some of the changes in individual values for the residual fat fraction are of interest. As is seen in Figure 6, changes in various subjects were not in the same direction at the same time. In subjects one and four at end of week 2, despite a sharp drop in cholesterol, there was a considerable rise in this fraction. Between week 4 and week 5, all individual cholesterol values rose, but residual fat increased sharply in two subjects (1 and 2), changed but slightly in two subjects (3 and 6), and dropped over 50 mg. per cent in two subjects (4 and 5). The trend in the mean value for this fraction was definitely down after two weeks of the 30 gm. animal fat, 70 gm. corn oil diet, but the decrease was not pronounced after week 4 in which total fat intake had been up to 170 gm. a day for one week. One more week of this regimen was followed by a scatter of individual values, making the small rise in mean value difficult to interpret. A

definite pattern may have emerged had this portion of the experiment been prolonged.

The general pattern of change expressed as per cent of mean total lipid made up by the means of each of the major fractions may be seen in Figure 7.

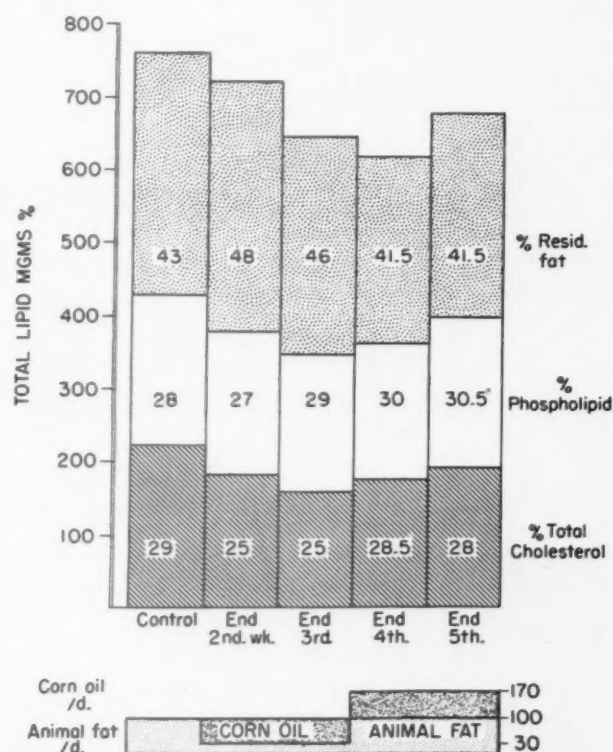


FIG. 7. Pattern of change expressed as per cent of mean total lipid made up by the means of each of the major fractions.

Allen Lipid (Table I, Fig. 8). It can be readily seen that this method gives results which parallel total lipid values measured by the gravimetric technic. Since a group of such determinations, giving internally reproducible results, may be carried out in an hour, it should prove useful as a screening procedure as well as a means by which to follow gross changes in total lipid.

Beta Lipoproteins (Table I, Fig. 9). The beta lipoproteins throughout the study gave from 60 to 80 per cent of the total color. The control mean was 73.3 per cent. After one week on the 70 gm. corn oil, 30 gm. animal fat diet (week 2) the mean was 70.9 per cent ($p < .1$). After the second such week (week 3), however, the mean was 68.5 per cent ($p < .02$). At the end of week 4 and of week 5 in which 100 gm. animal fat, 70 gm. corn oil was ingested, the mean values were 67.9 per cent ($p < .01$) and 67.7 per cent ($p < .02$), respectively.

It is noted that the changes in beta lipoproteins (and the reciprocal changes in alpha

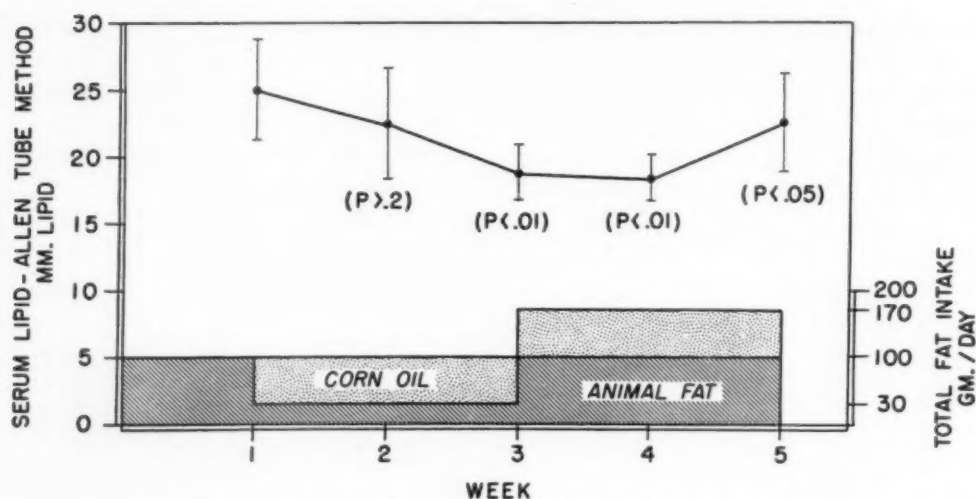


FIG. 8. Mean changes in Allen lipid.

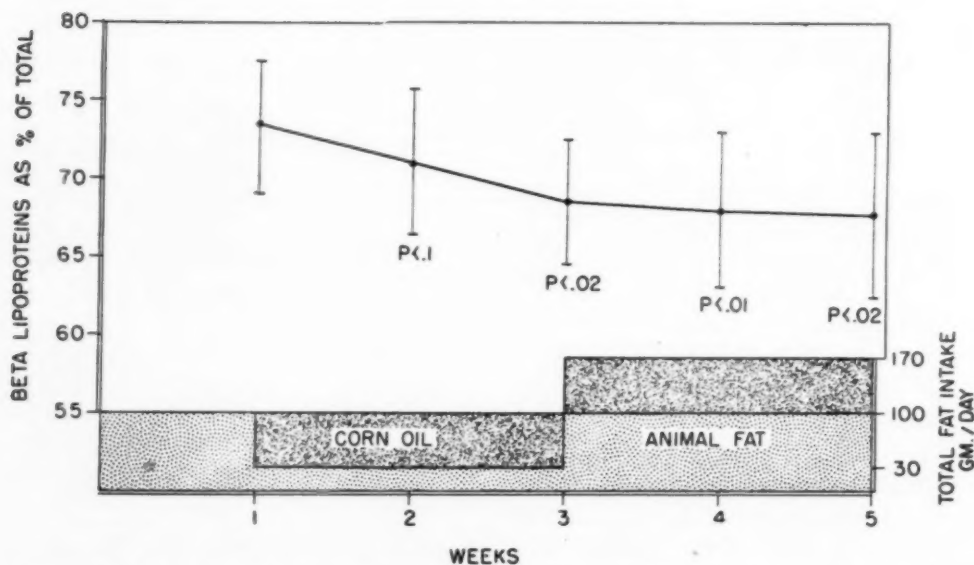


FIG. 9. Behavior and significance of mean values for serum beta lipoproteins, expressed as per cent of total lipoproteins.

fraction as well as in any calculated beta/alpha ratios) were not as dramatic as were the changes in cholesterol. In addition, the significant changes lagged behind cholesterol by one week, but maintained significant depressions below the control despite the higher total fat intake during weeks 4 and 5 when corn oil made up 41 per cent of the fat calories.

Iodine Numbers (Table 1, Fig. 10). Despite the fact that Hanus' reagent is said to give variable results in the presence of cholesterol [42], duplicate determinations on total lipid gave close agreement in our laboratory. The iodine number determinations were carried out on total petroleum ether-extractable lipid rather than on the saponifiable fraction. Thus the values for the iodine number are lower than

many in the literature [43-46], although they do come into the range given by Czonka [47] as well as by Nicholls and Perlzweig who also used Hanus' reagent [48]. The lower numbers on unsaponified total lipid are to be expected because of the presence of materials taking up relatively little or no iodine, namely: choline, glycerol, phosphoric acid and cholesterol (theoretic iodine number of the latter = 66) [44].

In the present study the lowest value was 68.3 and the highest 84.4. In the presence of considerable amounts of materials that will take up little or no iodine, large changes in degree of unsaturation of the constituent fatty acids may manifest relatively small changes in the total iodine number of the material analyzed.

The control mean was 71.8, and after one

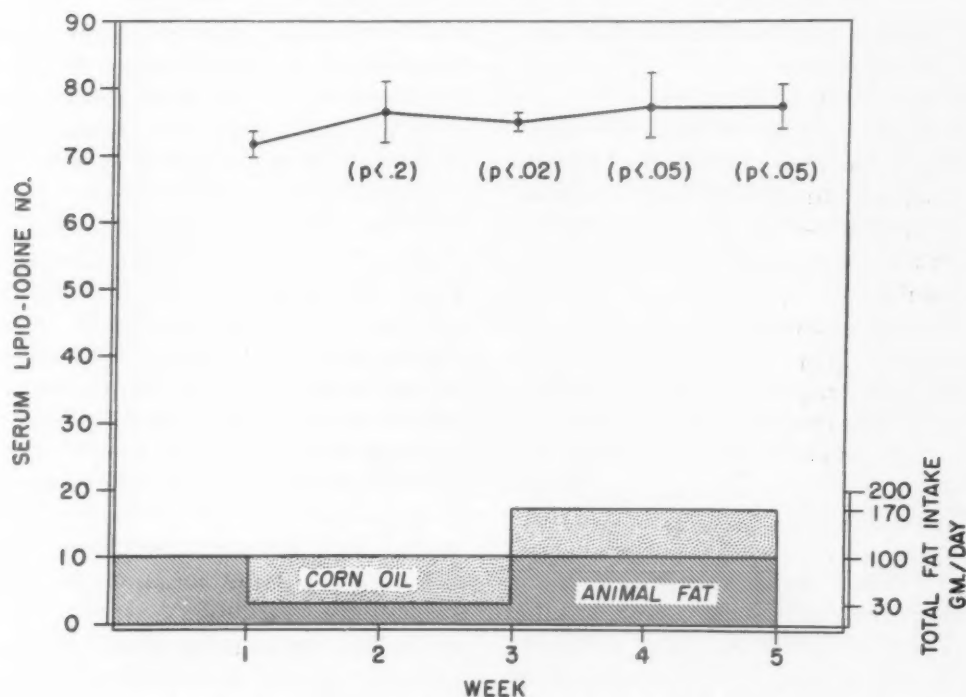


Fig. 10. Changes in mean values for total serum lipid iodine number.

week on 30 gm. animal fat, 70 gm. corn oil increased to 76.6 ($p < .2$). After two weeks on this regimen the value was 75.1 ($p < .02$). When total fat intake per day increased to 170 gm. of which 41 per cent was corn oil and 59 per cent was animal fat, there was a mean of 77.6 ($p < .05$) after one week (week 4) and a mean of 77.5 ($p < .05$) after two weeks (week 5). Thus the small but definite increases in iodine number of total lipid were well maintained after two weeks' resumption of the higher fat intake.

COMMENTS

The present study confirms previous results indicating that the ingestion of unsaturated oil can produce striking changes in serum lipids. The most striking changes were obtained when animal fat was restricted to 30 gm. per day, with corn oil supplying 70 per cent of total fat calories. When caloric and total fat intake were increased, and the percentage of fat supplied as corn oil was reduced from 70 per cent to 41 per cent, all values drifted toward control values within two weeks except for iodine numbers and beta lipoprotein percentage. From these data one concludes that maximum serum lipid depression secondary to corn oil ingestion occurs when total fat intake does not exceed 100 gm. per day, of which 70 per cent is corn oil. This ratio of unsaturated to saturated fat with respect to its effect on chole-

sterol level agrees closely with that noted by Beveridge [17].

The present data offer no comparison of the effects on serum lipids of corn oil with those of a fat-free regimen. Using a formula diet, Beveridge showed that corn oil acutely depressed cholesterol beyond the drop noted on a fat-free regimen [9]. This is also in agreement with the data of Bronte-Stewart et al. [13].

It appears that free and total cholesterol are the most labile of the lipids measured. Rapid, sharp changes have been observed by others [1-14]. In the present study, free cholesterol fell to an even greater degree than total cholesterol, the free:total ratio being significantly decreased throughout the period of corn oil ingestion. Decreases in cholesterol on the rice diet [49,66] and on low fat diets [50] were not associated with similar changes in free:total cholesterol ratio. Whether this is due to preferential enhancement of excretion or to greater ease of esterification in the presence of abundant linoleic acid, or to other reasons, cannot be determined from these data.

Phospholipid was less labile, changing more slowly and to a lesser degree than cholesterol. This agrees with observations of Best et al. in studies on the effects of beta sitosterol [51,52]. Kinsell has recorded more striking changes, closely paralleling cholesterol, with the feed-

ing of large amounts of vegetable fats [6]. Cholesterol/lipid phosphorus ratios were decreased by corn oil feeding in this study.

Depression of beta lipoproteins also lagged behind that of cholesterol, but these changes retained significance throughout the period of corn oil intake despite resumption of the larger animal fat intake during the last two weeks. The relative stability of phospholipid may be responsible for the relatively small changes in the mean values for beta lipoprotein. The data give no information on possible shifts in cholesterol from the beta to the alpha fraction.

On the whole, mean changes in total lipid may be largely accounted for by the shifts in cholesterol and phospholipid. Nevertheless, so-called residual fat (total lipid minus cholesterol and phospholipid) yielded mean values below the controls during the last three weeks of the experiment. Further studies aimed at delineating the pattern of neutral fat response during unsaturated oil ingestion would be of interest. It would appear that this fraction does not always follow the pattern of other lipid constituents.

That the iodine numbers increased and maintained this rise bespeaks a change in the fatty acid composition of various fat fractions. This study gives no information as to whether or not this change occurred preferentially in one or another of the lipid fractions. Part of the rise in iodine number may, of course, be accounted for by the sharp decreases in cholesterol (theoretic iodine number = 66). The maintenance of this rise during the last two weeks together with the fact that cholesterol at that time made up the same percentage of the total lipid as it did initially (Fig. 7) rules this out as the sole explanation for these observations. It seems likely that the major portion of this change is due to incorporation of linoleic acid or a derivative (arachidonic acid [53]) into the esters present in serum lipids. Linolenic acid, which is present in very small amounts in corn oil, may also contribute slightly.

The material or materials in unsaturated oils producing depression of serum lipids and its mechanism or mechanisms of action have been the subject of considerable discussion [13,15,16,54-56]. The questions raised have no definite answers as yet. One investigator has concluded that the active ingredient is linolenic acid [15]. The fact that this acid is absent in cottonseed oil despite the reported efficacy of this oil in lowering blood fats [2] makes this improba-

ble. Jones et al. [57] recently presented evidence that whole corn germ is more effective in cholesterol-fed chicks than the commercially available corn oil utilized in the present study. Yet in human subjects, Kinsell [58] produced dramatic, rapid lowering of cholesterol and phospholipid together with great rises in iodine number by feeding 40 to 50 gm. of ethyl linoleate per day. With the recent interest in highly unsaturated oils, it is of interest that Lever et al. produced depressions of serum lipids by intravenous administration of 10 per cent cottonseed oil or synthetic triolein in normal subjects as well as in patients with idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis [59].

Impressive changes in cholesterol have been reported in human subjects on low fat diets [23,50,60,67], large amounts of nicotinic acid [61,62], hot alcoholic extract of mammalian brain [63], phytosterols [51,52], estrogens [64,75], intravenous and oral calcium EDTA [66], corticotrophin, cortisone, L-thyroxine, L-triiodothyronine, triiodothyroacetic acid [75], as well as by ingestion of unsaturated oils. A single common denominator is probably not present.

A mechanism of action is not apparent from our own data. In rats on fat-free, cholesterol-free diets, palmitic and stearic acids have been demonstrated to enhance endogenous cholesterol excretion while corn oil did not [65]. Certainly not enough phytosterols are present in corn oil to produce the effects reported by others (about 0.75 per cent).

Relative essential fatty acid (E.F.A.) deficiency has been implicated as a common pathologic state leading to, among other things, the formation of "abnormal" cholesterol esters and a tendency for their deposition [13,16]. Indeed, Peifer and Holman have shown that in rats fed cholesterol on an E.F.A.-deficient diet symptoms of E.F.A. deficiency develop sooner than in those not given cholesterol. This suggested an affinity between E.F.A. and cholesterol, with accelerated transport and rapid depletion of E.F.A. in hypercholesteremic states. Alfin-Slater et al. demonstrated decreased serum cholesterol and increased deposition of cholesterol esters in liver and adrenal in E.F.A.-deficiency states in rats [69]. Wood and Migicovsky found linoleic acid twice as effective as oleic acid in inhibiting cholesterol synthesis by liver homogenates from rats [70].

It appears established that the most abundant poly-unsaturated fatty acid of plasma is linoleic

acid, with its potential derivative arachidonic acid next [15], and in cells these positions of relative abundance are reversed [45,71]. Comparing persons with atherosclerotic disease to blood bank donor control subjects of comparable age, Hammond and Lundberg found increased amounts of total fatty acids in the diseased individuals but a decreased percentage of 2 and 4 double bond acids (linoleic and arachidonic) and increases in the 3 double bond acid (linolenic) [77]. Hansen et al. found absolute decreases in 2 and 4 double bond together with increases in 3 double bond acids in the serums of infants on low-fat diets. In spite of these observations, there are no conclusive data which would indicate that human atherosclerosis is secondary to a deficiency of certain fatty acids.

The most abundant material in corn oil is linoleic acid (56.2 per cent of total), which has been shown capable of condensation to arachidonic acid in vivo in rats [53,73]. This reaction is apparently catalyzed by pyridoxine in rats on E.F.A.-deficient diets [74]. If unequivocal linoleic and arachidonic acid deficiencies can be substantiated in disease, a rationale for the administration of oils rich in these substances would be provided. Carboxy-labelled C¹⁴ linoleate fed to mice, however, has been picked up in cholesterol [73].

In general, it appears as if the low serum cholesterol in a variety of populations partaking of low-fat diets is associated with a low incidence of myocardial infarction [18-23,27-29]. The feeding of various unsaturated oils certainly accomplishes lowering of cholesterol even under conditions of great activity and particularly when animal fat is restricted, as shown in this and other studies [1-14]. Longer term pilot studies in our laboratory indicate that even on a somewhat more liberal animal fat intake than 30 gm. per day average cholesterol values may be maintained below control levels during full activity as long as the corn oil emulsion is taken.

That multiple factors are involved in the etiology and pathogenesis of human coronary artery disease there can be no doubt. The role of the unsaturated oils in the treatment or prevention of this complex disorder is still far from clear.

SUMMARY

1. The serum lipids of six normal young men on diets of varying fat composition were studied.
2. When 70 per cent of fat intake was made

up by corn oil and the total fat restricted to 100 gm. per day, impressive depressions of all serum lipid fractions were recorded.

3. All fractions tested, except beta lipoproteins and iodine numbers, tended to return toward control values when calories and total fat intake were increased, and the per cent of total fat made up by corn oil decreased to 41 per cent.

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Studies in Cushing's Syndrome*

I. Observations on the Response of Plasma 17-Hydroxycorticosteroid Levels to Corticotropin

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THE nature of the primary lesion in Cushing's syndrome associated with bilateral adrenal cortical hyperplasia has never been satisfactorily defined. Since the administration of adrenal cortical steroids can produce all the features of the syndrome, there is general agreement that the clinical picture is caused by adrenal overproduction of steroids, e.g., cortisol. But the question of whether the fundamental derangement resides in the hypothalamus, in the anterior pituitary or in the adrenal cortex has remained a matter for dispute [1-6].

Recent studies in several laboratories have shown a characteristic abnormality in most patients with this disorder. Laidlaw et al. [7], using urinary corticosteroid values as a parameter, Grumbach et al. [6], Christy et al. [8] and Lindsay et al. [9] measuring plasma 17-OH-corticosteroid levels, have all demonstrated that the administration of corticotropin usually causes excessive rises in steroid values. This hyperresponsiveness of the adrenal cortex could be interpreted as evidence suggesting that an intrinsic adrenocortical disease may be the basic lesion.

The purpose of these studies was to characterize the exaggerated response of the hyperplastic adrenal cortex in more detail, and to compare this response with that of adrenal cortical tumors. Data were obtained which suggest that the concept of an intrinsic adrenal cortical lesion is perhaps inadequate to explain the pathogenesis of bilateral adrenal hyperplasia.

MATERIALS AND METHODS

Fifteen patients, four males and eleven females, ranging in age from eight to fifty-seven years, were

diagnosed as having Cushing's syndrome without adrenal tumor on the basis of the typical clinical picture and abnormal laboratory findings, including elevated levels of plasma or urinary corticosteroids. In no patient was a suprarenal mass seen by x-ray, nor was an adrenal tumor found in the thirteen patients who were subjected to operation. In these thirteen patients there was histologic evidence of adrenocortical hyperplasia. Under a variety of conditions, to be described, all fifteen individuals were tested by means of an infusion of 25 U.S.P. units of ACTH in a manner previously set forth [8]. Plasma 17-OH-corticosteroid levels were determined by the method of Silber and Porter [10] as modified in this laboratory [11].

Similar studies were performed in two patients with Cushing's syndrome due to benign adrenal adenoma and in four patients with adrenal cortical carcinoma. In all six patients the diagnosis was proved by operation.

RESULTS

Excessive Response of the Adrenal Cortex to ACTH.

The response of patients with bilateral adrenal hyperplasia to a standardized ACTH infusion is shown in Figure 1. In fourteen of the fifteen patients the average plasma 17-OH-corticosteroid level at the termination of the four hour corticotropin infusion was 81 $\mu\text{g.}/100\text{ ml.}$ (range 61 to 118 $\mu\text{g.}/100\text{ ml.}$). This is in contrast to post-ACTH levels in forty normal subjects which averaged 46 $\mu\text{g.}/100\text{ ml.}$ (range 35 to 55 $\mu\text{g.}/100\text{ ml.}$) [12]. The difference in mean increments (Cushing's syndrome, 54; normal, 29) was statistically significant ($P < .001$).

In the fifteenth patient two ACTH tests revealed normal plasma 17-OH-corticosteroid response, with rises from 16 to 53 $\mu\text{g.}/100\text{ ml.}$ and from 29 to 49 $\mu\text{g.}/100\text{ ml.}$ After two days

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of intravenous ACTH administration a third ACTH test showed an exaggerated response, with plasma corticosteroid rise from 24 to 83 $\mu\text{g.}/100\text{ ml.}$ *

The abnormally elevated post-ACTH level of circulating 17-OH-corticosteroids found in these

patients probably cannot be ascribed to delayed disposal of cortisol from the plasma. In two patients intravenously administered stable cortisol (100 mg.) disappeared from plasma at a rate comparable to that exhibited by normal subjects ("half-time" in two patients with

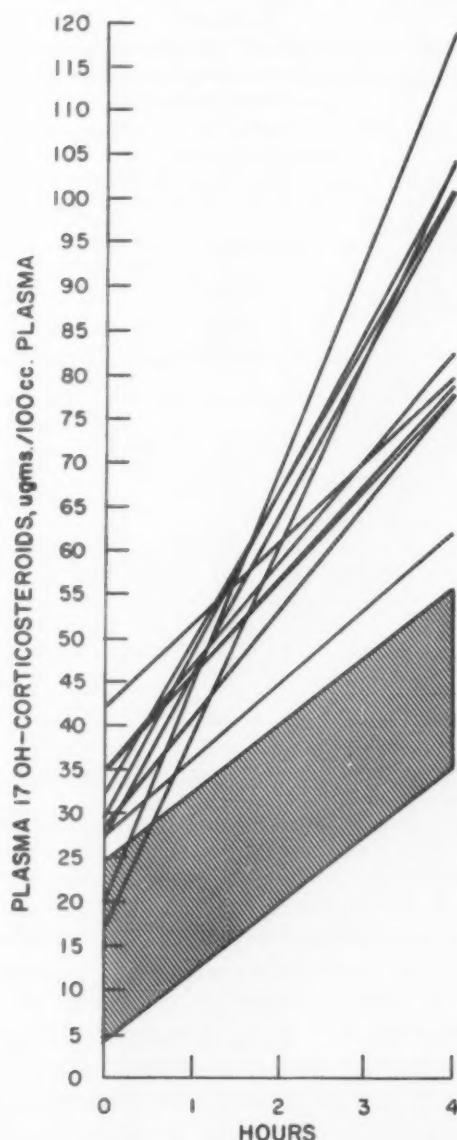


FIG. 1. Response of plasma 17-OH-corticosteroid levels to intravenous ACTH in eleven patients with Cushing's syndrome associated with bilateral adrenocortical hyperplasia (solid lines) compared with response in forty normal subjects (shaded area).

* It is perhaps pertinent that no example of exaggerated response to ACTH of free (unconjugated) plasma 17-OH-corticosteroid levels could be shown in five patients treated with varying doses of corticotropin (4 to 80 U.S.P. units) over brief or prolonged periods of time (3 days to 5 years). Comparable results have been reported by BAYLISS and STEINBECK [13].

DECEMBER, 1957

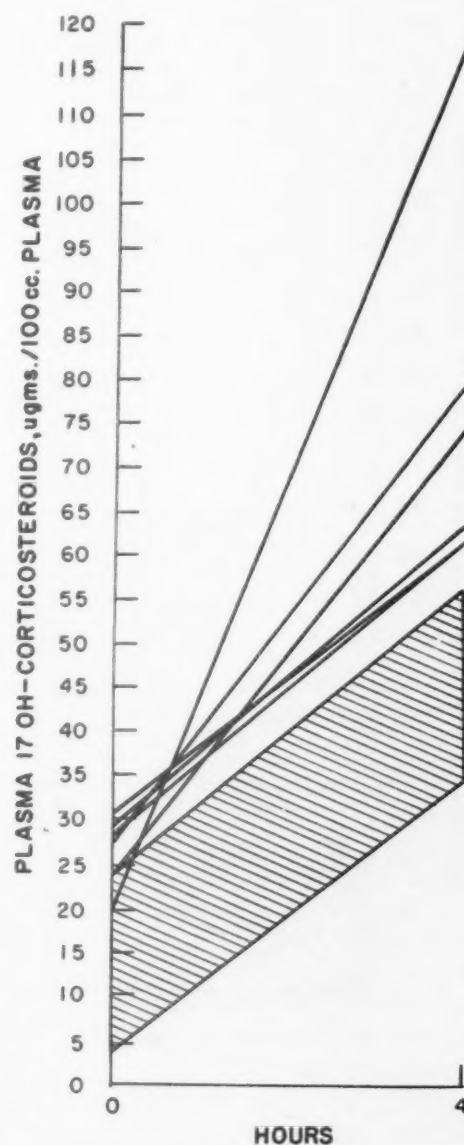


FIG. 2. Effect of unilateral adrenalectomy upon excessive response of plasma 17-OH-corticosteroid levels to intravenous ACTH in patients with bilateral adrenal hyperplasia (solid lines). Range of normal response is represented by the shaded area.

bilateral adrenal hyperplasia averaged two hours; in twenty normal subjects reported by Peterson et al. [14] "half-time" averaged 1.9 hours, a figure similar to the average of 2.2 hours found in a small group of normal subjects in this laboratory).

Figure 2 shows the effect of unilateral adrenalectomy upon this exaggerated response to ACTH of the hyperplastic adrenal cortex. In six patients tested with corticotropin several months after unilateral adrenalectomy the average post-ACTH level of plasma corticosteroid was 76 $\mu\text{g.}/100 \text{ cc.}$

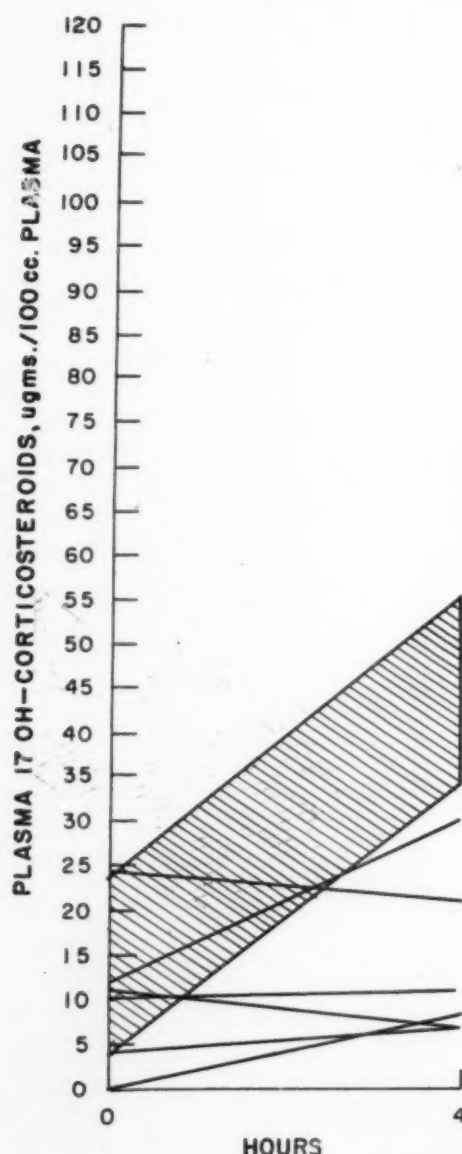


FIG. 3. Effect of bilateral subtotal adrenalectomy upon adrenocortical response to intravenous ACTH in patients with bilateral adrenal hyperplasia (solid lines). Range of normal response is represented by the shaded area.

100 ml. (average increment, 50 $\mu\text{g.}/100 \text{ ml.}$ as compared to 54 $\mu\text{g.}/100 \text{ ml.}$ in the unoperated group). This value is only slightly less than that found before operation (81 $\mu\text{g.}$ per cent), and the difference is in fact within the limits of error of the method [17]. The finding of persistent hyper-response in the face of removal of about 50 per

cent of adrenal tissue is interesting in that it suggests the relative unimportance of adrenal mass *per se* as an essential factor in the abnormality. A further indication of the relatively minor role of excess adrenal mass is gained from the observation that in one patient in this

TABLE I
EFFECT OF PREDNISONE ADMINISTRATION UPON
ADRENOCORTICAL RESPONSE TO EXOGENOUS
ACTH IN PATIENTS WITH CUSHING'S
SYNDROME DUE TO BILATERAL
ADRENAL HYPERPLASIA
(Plasma 17-OH-corticosteroids, $\mu\text{g.}/100 \text{ ml.}$)

Patient	Before Prednisone		After Prednisone	
	Before ACTH	After ACTH	Before ACTH	After ACTH
S. B.	34	76	43	85
D. W.	27	79	37	84
A. C.	35	82	32	79
M. S.	27	100	23	60
F. S.	16	103	47	94
S. L.	29	103	26	79
Average:	28	90*	35	80*
B. W.†	42	79	28	49

* Mean increments 63 and 46 $\mu\text{g.}/100 \text{ ml.}$ before and after prednisone, respectively; $P > 0.05$, no significant difference.

† This patient received 9-alpha-fluorohydrocortisone (see text), and her data are not included in the averages in this table.

group the combined weight of both adrenals was within normal limits. However, if enough adrenal tissue is removed (90 to 95 per cent) the phenomenon of hyper-response disappears, as one might anticipate and as is shown by the subnormal plasma corticosteroid responses found in six patients subjected to bilateral subtotal adrenalectomy. (Fig. 3.)

Effect of Prednisone upon Adrenal Cortical Hyper-response to ACTH. Earlier studies had shown that patients with Cushing's syndrome due to bilateral adrenal hyperplasia, unlike those with adrenal tumor, sometimes exhibited falls in urinary 17-ketosteroid levels when cortisone was administered, suggesting a degree of "pituitary dependence" of the hyperplastic adrenal cortex [15]. Six patients in the present group were given prednisone in doses of 30 to 50 mg. daily for periods of four to eight days. Instead of

measurements of urinary 17-ketosteroids, standard ACTH tests were performed before and after the course of prednisone. Smaller doses of prednisone, 20 to 30 mg. per day for seven days, have been shown to suppress adrenocortical response to exogenous ACTH in normal sub-

drome (with adrenal hyperplasia) who received roentgen therapy to the pituitary region. The results are summarized in Table II. One patient (N. C.) was tested before pituitary radiation and again five and twelve months after treatment. In this subject the change in adrenal responsive-

TABLE II
EFFECT OF PITUITARY RADIATION IN BILATERAL ADRENAL HYPERPLASIA. RESPONSE OF PLASMA 17-OH-CORTICOSTEROID LEVELS TO EXOGENOUS ACTH BEFORE AND AFTER PITUITARY RADIATION

Patient	Plasma 17-OH- corticosteroids (μg. %)		Time Elapsed after Radiation	Remis- sion	Plasma 17-OH- corticosteroids (μg. %)	
	Before Radiation				After Radiation	
	Before ACTH	After ACTH			Before ACTH	After ACTH
N. C.	..	80	5 months	Partial	22	63
	12 months	Yes	12	38
F. S.	16	103	8 months	No	28	94
S. L.	29	103	6 weeks	No	23	97
B. W.	43	79	6 months	No	42	60
M. diT.	3 years	Yes	9	55
C. T.	6 years	Yes	29	54

jects [12]. After prednisone, rises in plasma 17-OH-corticosteroid levels during ACTH infusion were subnormal. In contrast to these normal individuals the patients with Cushing's syndrome continued to show excessive responses to ACTH, although responses in two instances were less exaggerated than those found in the pre-prednisone tests. The results are shown in Table I. In one patient, an eight year old girl who received the still more potent steroid, 9- α -fluorohydrocortisone, in doses of 6 mg. daily for three days, there was more suppression of the excessive response. Even in this case, however, the inhibition was not as great as in normal subjects, the post-prednisone response being in the normal range rather than in the subnormal (patient B. W., Table I).

Effect of Pituitary Radiation upon Adrenal Cortical Hyper-response to ACTH. While some of the data cited might be interpreted as suggesting an inherent disorder of the adrenal cortex, they cannot easily explain why measures which presumably reduce pituitary activity are sometimes associated with clinical remission. Studies of plasma corticosteroid response to ACTH were carried out in six patients with Cushing's syn-

TABLE III
EFFECT OF ACTH ADMINISTRATION UPON PLASMA 17-OH-CORTICOSTEROID LEVELS IN PATIENTS WITH ADRENAL CORTICAL CARCINOMA OR ADENOMA

Patient	Sex	Age (yr.)	Diagnosis	Plasma 17-OH-corticosteroids (μg./100 ml.)	
				Before ACTH	After ACTH
H. S.	F	28	Adenoma	26	34
				50	51
V. C.	F	39	Adenoma	40	45
				34	43
L. T.	F	52	Carcinoma	46	62
L. R.	F	46	Carcinoma	40	42
A. G.	F	37	Carcinoma	68	56
G. L.	M	6 mo.	Carcinoma	36	73

ness toward normal was associated with a clinical remission. Three additional patients were studied before and again one and a half to eight months after completion of a course of pituitary radiation (F. S., S. L. and B. W. Table II). In these three, persistence of excessive responsiveness of the adrenal to ACTH was associated with persistence of clinical hyper-adrenocorticism, although B. W. showed a less markedly exaggerated response to ACTH than in the control period. In the last two patients shown in Table II (M. diT., C. T.), studies were made during prolonged clinical remissions three and six years after x-ray treatment. Responses to ACTH were normal. However, one hesitates to ascribe too much significance to the data obtained from these last two patients, since no pretreatment studies were performed.

Adrenal Cortical Tumors. It should be emphasized that the excessive response to ACTH found in most patients with bilateral adrenal hyperplasia does not provide an infallible differential diagnostic aid in excluding adrenal cortical tumor. In one of four patients with proved adrenal cortical carcinoma (G. L., a six month old boy, Table III) who was tested as described, the response to corticotropin was ex-

cessive. This finding modifies a statement made earlier from this laboratory on the basis of the few data then available [8]. The remaining three patients with adrenal carcinoma (Table III) showed limited response or no response at all to administered ACTH. Similarly, the two patients with benign adrenal cortical adenoma showed little response to ACTH although plasma 17-OH-corticosteroid levels were generally elevated.

Adrenal Cortical Response to ACTH in Severe Illness. Standard ACTH tests were performed upon 128 patients with a variety of chronic diseases. Plasma 17-OH-corticosteroid responses were within normal limits in 115 patients. However, in thirteen subjects, who were severely ill and in some instances moribund, exaggerated responses were found. Pre-ACTH plasma corticosteroid levels in these thirteen subjects averaged 30 $\mu\text{g.}/100\text{ ml.}$ (average of normal subjects 16 $\mu\text{g. per cent}$ [17]) with an average of 80 $\mu\text{g.}/100\text{ ml.}$ after administration of corticotropin. These responses are quantitatively comparable to those found in the patients with bilateral adrenal hyperplasia. There was no serious clinical question of hyperadrenocorticism in any of the severely ill patients, and indeed the adrenals were normal in weight and morphology in the two patients examined postmortem. These data are presented merely to emphasize the fact that exaggerated plasma 17-OH-corticosteroid response to ACTH is not unique in or diagnostic of Cushing's syndrome with bilateral adrenal hyperplasia. No entirely satisfactory explanation for the hyper-response found in these thirteen patients can be offered at this time. It is possible that the elevated resting and post-ACTH plasma steroid levels may be due in part to the delayed disappearance of cortisol from plasma which has been described in moribund patients [16].

COMMENTS

From some of the data presented herein, and from earlier studies [4-6], there emerge certain findings which suggest that the basic defect in Cushing's syndrome associated with bilateral adrenal hyperplasia is a primary disorder of the adrenal cortex. The characteristic hyper-response to exogenous corticotropin [6-9], and the persistence of this excessive response after unilateral adrenalectomy and after administration of prednisone are in keeping with this hypothesis.

There are other data which can be interpreted

as supporting either an adrenal or pituitary origin of bilateral adrenal hyperplasia. At first sight, it would appear that the occasional clinical remissions induced by procedures aimed at reducing anterior pituitary function (electrocoagulation [17], pituitary radiation [18-20], hypophysectomy [21]) tend to favor a pituitary etiology of the disease. However, it should be borne in mind that the pituitary may function in this disease merely as a supporting or sustaining influence [21], so that clinical improvement following hypophyseal radiation or surgery does not necessarily constitute evidence against the possibility that the primary defect is in the adrenal cortex. A further argument against a pituitary etiology of adrenal hyperplasia is the failure of several investigators to detect excessive quantities of pituitary adrenocorticotrophic hormone in the plasma of patients with the disease [22-24].

There is some circumstantial evidence which appears to support the hypothesis that the primary lesion may be in the anterior pituitary. Liddle *et al.* [25] have claimed that an adrenal weight-maintaining substance of equine pituitary origin can enhance the sensitivity of the adrenal cortex to the steroidogenic action of "orthodox" ACTH. The adrenal cortical hyper-responsiveness which can be induced in human subjects by this material is suggestive of that observed in patients with bilateral adrenal hyperplasia. If it is assumed that such an adrenal weight-maintaining corticotropin is secreted by the pituitary in bilateral adrenal hyperplasia, one might reconcile the apparent contradictions implied by the findings of persistent hyper-response after unilateral adrenalectomy and after administration of prednisone on the one hand, and failure to detect excessive amounts of "orthodox" ACTH in the patients' plasma on the other. There is no direct evidence at present which would indicate that the adrenal cortical hyper-responsiveness in this form of Cushing's syndrome can be ascribed to such a hypophyseal ACTH-potentiating factor. However, the postulate is intriguing, and speculations based upon it have been presented elsewhere [26].

In patients with Cushing's syndrome due to an adrenocortical tumor exaggerated response to administered ACTH is usually not found. In the present series only one patient of six showed such a response (G. L., Table III). However, there have been additional isolated reports in the literature of patients with benign or

malignant adrenal tumors who have responded excessively to exogenous corticotropin [9,27,28]. On the other hand, Knowlton, Pool and Jailer [29] were unable to demonstrate a suppressive effect of complete hypophysectomy upon the manifestations of hyperadrenalism in a patient with adrenal cortical carcinoma. This finding can be interpreted as implying a certain degree of autonomy of that adrenal neoplasm [29]. In contrast, hypophysectomy was followed by clinical remission in the patient with bilateral adrenal hyperplasia reported by Luft, Olivecrona, Ikkos and Hernberg [27]. A unifying hypothesis which can account for these apparently discordant observations is not forthcoming at this time.

SUMMARY

1. The exaggerated response to ACTH of the adrenal cortex in Cushing's syndrome associated with bilateral adrenocortical hyperplasia has been confirmed in fourteen of fifteen patients with the disease. The excessive response persisted after unilateral adrenalectomy.

2. In contrast to normal subjects, the excessive adrenal cortical response in six patients with bilateral adrenal hyperplasia proved relatively resistant to suppression by the administration of prednisone.

3. Limited data suggest that in patients with adrenal hyperplasia who experienced clinical remissions following pituitary radiation, the adrenal cortical response to ACTH reverted toward normal. In three patients who did not improve clinically after pituitary radiation, adrenal cortical response remained excessive.

4. Thirteen severely ill patients who exhibited no clinical evidence of adrenal cortical hyperfunction showed excessive plasma 17-OH-corticosteroid responses to ACTH which were quantitatively similar to those occurring in the patients with bilateral adrenal hyperplasia.

5. In five of six patients with Cushing's syndrome associated with adrenal cortical adenoma or carcinoma, exaggerated plasma 17-OH-corticosteroid response to ACTH did not occur.

Acknowledgments: The authors are grateful to the following physicians for the referral of patients for study: Dr. John Sandson, Albert Einstein College of Medicine and the Bronx Municipal Hospital; Dr. Martin Perlmutter, the Maimonides Hospital, Brooklyn, N. Y.; Dr. Helen B. Horowitz, Montefiore Hospital, Bronx,

N. Y.; Dr. Herbert Koteen, New York Hospital; and Drs. Abbie I. Knowlton, Felix E. Demartini, Melvin M. Grumbach, Calvin H. Plimpton and Sidney C. Werner of the Presbyterian Hospital. Thanks are also due to Miss Elsie C. Ewen for her skilled technical assistance. Generous supplies of materials were made available by Armour, Inc., Organon, Inc. and the Upjohn Company.

ADDENDUM

Since the preparation of the manuscript, studies have been made upon two additional patients with Cushing's syndrome and bilateral adrenal hyperplasia. Both patients showed excessive plasma 17-OH-corticosteroid responses to ACTH which reverted to normal several months after pituitary radiation, in association with clinical improvement.

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The Agammaglobulinemias*

Relations and Implications

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APPROXIMATELY 25 gm. of an endogenous polyvalent "antibiotic," gamma globulin, circulates in the normal bloodstream, and its absence is, with occasional exceptions, accompanied by a striking predisposition to infection. Three forms of this unique metabolic disturbance, agammaglobulinemia, have been described: (1) a physiologic or transient form occurring in early infancy, (2) a congenital form inherited as a sex-linked recessive trait in males, and (3) an acquired form, occurring in adults of either sex. In addition, agammaglobulinemia may accompany a limited number of disease states in which the protein disturbance is secondary. For convenience, agammaglobulinemia (congenital or acquired) which occurs as a solitary defect in protein metabolism unassociated with other diseases may be referred to as primary. (Table I.)

Primary agammaglobulinemia is uncommon. In Moncke's electrophoretic study of 6,000 serums from persons aged fifteen years and over, the absence of gamma globulin was encountered [1] only once. Since Bruton's original description of primary agammaglobulinemia in 1952 [2] approximately sixty cases have been reported, and from these reports a distinctive syndrome has emerged.

The cardinal clinical characteristics of primary agammaglobulinemia are: (1) an extraordinary susceptibility to infections, (2) good response of individual infections to antibiotic therapy, as contrasted to (3) usual failure of antibiotic prophylaxis, even though resistant bacteria are not involved. Certain clinical sequences such as repeated pneumonias and sprue-like syndromes are particularly suggestive of agammaglobulinemia. To these should proba-

bly be added, as useful clinical mnemonics, the occurrence of influenzal meningitis in an adult, herpes zoster, hematologic abnormalities including neutropenia, lymphopenia and hypersplenism, and failure of the erythrocyte sedimentation rate to rise appropriately during acute infection.

TABLE I
THE AGAMMAGLOBULINEMIAS

- | |
|-------------------------------------|
| i. Physiologic—in early infancy |
| ii. Primary |
| 1. Congenital—in male children |
| 2. Acquired—in adults of either sex |
| iii. Secondary to |
| 1. Hypoproteinemia |
| (1) Congenital panhypoproteinemia |
| (2) Transient dysproteinemia |
| (3) Hepatic disease |
| (4) Nephrosis |
| (5) Malnutrition |
| (6) (?) Sprue |
| 2. Neoplasms |
| (1) Multiple myeloma |
| (2) Lymphoma |
| (3) Lymphatic leukemia |
| (4) (?) Thymoma (benign) |

Characteristic laboratory findings in primary agammaglobulinemia include absence of gamma globulin, absence of isohemagglutinins, failure to form antibodies following antigenic challenge, and absence of plasma cells from the bone marrow.

Recognition of agammaglobulinemia not only offers a diagnostic challenge but also has practical importance in that patients with this malady may die despite antibiotic therapy, if their need for gamma globulin is not discovered.

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The following case illustrates the salient features of acquired agammaglobulinemia.

CASE 1. A fifty-three year old housewife had enjoyed good health until September, 1953, when cough, chills and fever developed. These symptoms occurred irregularly for two months before she consulted her physician. A roentgenogram of the chest showed dense opacification of the upper lobe of the right lung with elevation of the right hemidiaphragm. She had anemia, the erythrocytes numbering 3,640,000 per cu. mm. with a hemoglobin of 9.2 gm. per cent. The leukocyte count was 24,150 per cu. mm. with 90 per cent polymorphonuclears and 10 per cent lymphocytes. Sputum smears showed a mixed bacterial flora with no acid-fast bacilli or fungi. Agglutinations for typhoid, brucellosis and tularemia were negative. The clinical response to penicillin and tetracycline was rapid but roentgenograms of the chest during the next three months showed persistent infiltration in the upper lobe of the right lung. Bronchoscopic examination on March 10, 1954, and bronchial washings yielded no helpful information. Fever and leukocytosis recurred frequently during the next few months, with good response each time to various antibiotics.

In July, 1954, the patient was hospitalized after the sudden onset of severe headache, stiff neck, fever and delirium. The spinal fluid contained 12,500 leukocytes per cu. mm., predominantly lymphocytes; protein, 465 mg. per cent; sugar, 15 mg. per cent; and chloride, 630 mg. per cent. Hemophilus influenzae was cultured from the spinal fluid. After being comatose for forty-eight hours she responded to intensive therapy with streptomycin, sulfadiazine and penicillin. During the febrile period many large vesicles developed over the anterior trunk and left lower extremity. This was thought to be herpes zoster, and scars were left at the sites of the vesicles. Blood samples drawn on July 10, 15 and 23 were reported negative by the State Virology Laboratory for the viruses of Western equine encephalitis, St. Louis encephalitis and herpes. She had a remarkable leukopenia at the height of the infection, the white cell count being 2,600 per cu. mm. with 59 per cent polymorphonuclears, 40 per cent lymphocytes and 1 per cent monocytes.

On recovery from the meningitis and herpes zoster she was found to have a left foot drop, considerable unsteadiness in gait, dizziness, fearfulness, and some slowing of mentation. Pneumonia kept recurring, responding each time to penicillin and tetracycline.*

The patient was first seen at the Sansum Clinic in February, 1956, complaining of cough and irregular fever. The past history revealed that she had had the usual childhood diseases without complication. Eczematoid dermatitis had involved the face and arms sporadically, but she had been in excellent health for

at least two years prior to the first attack of pneumonia in September, 1953.

Physical examination disclosed a frail woman with an unsteady voice and a frequent dry cough. The only positive findings were moist rales at both lung bases and a complete left foot drop.

A roentgenogram of the chest showed basal infiltration in each lung. Despite this, the leukocyte count was only 7,900, with a normal differential. There was no anemia and serologic tests for syphilis were negative. The erythrocyte sedimentation rate was 51 mm. in one hour (Westergren). Urinalysis, bromsulphalein® test and serum alkaline phosphatase were normal. A blood smear for lupus erythematosus cells (Zimmer-Hargraves method) was negative. The spinal fluid contained 2 lymphocytes per cu. mm., 15 mg. per cent protein, and the gold curve was 000-0000000. Three blood cultures were negative. Sputum cultures were negative for acid-fast bacilli and fungi, and yielded a mixed flora including pneumococcus, Staphylococcus aureus, alpha streptococcus, Neisseria catarrhalis and H. influenzae. Skin tests with coccidioidin and first strength P.P.D. were negative. Repeat bronchoscopic examination and bronchograms were negative. Culture of bronchial washings yielded Streptococcus pyogenes and H. influenzae, which surprisingly were still sensitive *in vitro* to many antibiotics, including tetracycline.

As no anatomic reason for the recurring pneumonias was found, a program of antibiotic prophylaxis was initiated. She took mysteclin (tetracycline plus nystatin), four times daily, and remained free of fever for a month, with a gain of 6 pounds in weight. Because the chest roentgenogram showed only partial resolution of the bilateral pneumonia, prednisone, 5 mg. twice daily, was added to the therapeutic regimen. A roentgenogram of the chest on May 31, 1956 showed completely clear lung fields for the first time in nearly three years. Therapy was discontinued.

Two days after the last dose of antibiotic, fever recurred and the temperature reached 104°F. within three days. Mysteclin was promptly resumed and the fever subsided within forty-eight hours. She was advised to continue the antibiotic in prophylactic doses for an indefinite period.

At this point a serum protein electrophoresis was done. Absence of gamma globulin was demonstrated. Before the patient could be reached to institute therapy with gamma globulin, and while she was still taking mysteclin, fever and cough recurred. She rapidly grew worse despite an increase in dosage of the antibiotic. A roentgenogram of the chest showed recurrence of bilateral lower lobe pneumonia. The leukocyte count was only 11,900, with 5 per cent band forms, 70 per cent segmented forms, 24 per cent lymphocytes and 1 per cent monocytes. Blood cultures yielded an anaerobic beta hemolytic streptococcus sensitive (disc method) to several antibiotics, including tetracycline; the same organism was dominant in the sputum culture.

* We are indebted to Dr. R. Stewart Hiatt for making available the clinical record.

The patient was given 30 cc. of gamma globulin intramuscularly and oral chloramphenicol, 500 mg. every six hours. She became afebrile in forty-eight hours, and a roentgenogram of the chest taken on the tenth day showed clearing of both lung fields.

Additional studies were carried out because of her agammaglobulinemia. The blood was negative for cold agglutinins and autoagglutinins at 20°C. and at 37.5°C. Direct and indirect Coombs' tests were negative. Her blood was group O, Rh positive, but the serum contained no isohemagglutinins, as demonstrated by failure to agglutinate type A and B erythrocytes. She was given three injections of typhoid-paratyphoid vaccine, and repeat agglutinations showed total failure to form antibody. A bone marrow aspirate from the iliac crest showed normal proportions and maturation of the erythroid and myeloid series and absolute absence of plasma cells in the twelve smears examined.

After her recovery from pneumonia in July, 1956, the patient was given 30 cc. of gamma globulin intramuscularly each month; she remained free of symptoms until December, 1956. Two days after the injection of gamma globulin in December, fever and cough recurred. One week later a chest roentgenogram showed pneumonia in the middle lobe of the right lung. Therapy with mystecilin resulted in prompt control of the infection. In view of our inability to secure adequate protection with either an antibiotic or gamma globulin alone, prophylactic therapy with gamma globulin plus a triple-sulfonamide preparation is now being employed.

COMMENTS

Clinical Features. The original case of agammaglobulinemia reported by Bruton in 1952 occurred in a nine year old boy [2], and several additional cases reported later the same year [3] also occurred in male children. Primary agammaglobulinemia was thought to be a congenital disease, transmitted as a sex-linked recessive trait. This concept still remains valid for primary agammaglobulinemia in children, since the syndrome has not been described in a female child, and search among the male siblings of children with the syndrome has uncovered additional instances of agammaglobulinemia.

Sanford et al. [4] in 1954 first described primary agammaglobulinemia in an adult, and from subsequent reports it has become apparent that the syndrome may appear at any age. It is assumed that agammaglobulinemia in adult patients is acquired, and did not exist during the many years that good health was enjoyed. While in no case has this assumption been verified by an electrophoresis carried out before and after the syndrome of excessive vulnerability to infec-

tion appeared, Martin's [5] patient did have a normal serum total protein, albumin and globulin (Howe method) during the first year of her illness.

Vulnerability to infection in patients with agammaglobulinemia is especially striking with respect to bacterial invaders. The typical history is that of multiple bouts of pneumonia, frequently due to the same organism. Pneumonia occurred thirty-five times in one of the patients reported by Zinneman [6]. Bronchiectasis is so frequent in patients with agammaglobulinemia that a serum protein electrophoresis in all patients with bronchiectasis has been suggested as a case finding method for agammaglobulinemia [7]. Meningitis due to *H. influenzae*, which is characteristically a disease of children, has been reported in two other adults with primary agammaglobulinemia [1,4], and has occurred twice in the same patient [7].

Ancillary evidence of inability to cope normally with bacterial invaders is the consistent failure of serum agglutinins and positive skin reactions to develop in agammaglobulinemic patients following the administration of bacterial vaccines and antigens [8].

There is considerably less agreement concerning the vulnerability of agammaglobulinemic patients to viral infections. It has been stated that patients with agammaglobulinemia handle viral infections in a nearly normal manner [7]. However, Bruton's original patient had mumps three times and showed a negative mumps complement fixation test three weeks after the third attack [2]. Keidan's [9] patient died of generalized vaccinia following a routine vaccination for smallpox, and such a catastrophe has been reported in three other children with agammaglobulinemia [10,11]. On this basis Good [7] withholds vaccination from his patients with agammaglobulinemia, although Apt [12] has had no complications arising from vaccination in his experience with twenty-four agammaglobulinemic patients. One of Good's patients died of fulminant infectious hepatitis [7]. Several patients [1,5,13-15], including ours, have had herpes zoster, an incidence approaching 20 per cent of the reported adult cases, which would appear to be disproportionately high. In many cases of agammaglobulinemia incessant upper respiratory infections have figured prominently in the syndrome, and it is a reasonable assumption that some of these infections have been due to A.P.C. or A.R.D. viruses. On the other

hand the only antibody consistently recovered from Martin's [5] patient in a prolonged exhaustive study was Type 4 A.P.C. virus neutralizing antibody.

Recurrent diarrhea and a "sprue-like syndrome" have been described in several adults with acquired agammaglobulinemia. The relationship of the gamma globulin deficiency to the intestinal disturbance would appear to differ somewhat in each case. Martin's patient had several episodes of febrile diarrhea along with many other infections which were ascribed to the susceptibility to infection accompanying agammaglobulinemia [5]. In Sanford's [4] patient a reasonably complete sprue syndrome developed, with weight loss, cutaneous pigmentation, foamy stools, normochromic anemia, flat oral glucose tolerance curve, impaired vitamin A absorption, steatorrhea and a small intestinal roentgenographic pattern of puddling, segmentation and marginal irregularity. Hypoproteinemia is a frequent finding in well established sprue, and the very low serum proteins in this patient, 3.8 to 4.8 gm. per cent, with only 25 mg. per cent gamma globulin, may have been part of the sprue syndrome. The agammaglobulinemia may therefore be secondary rather than primary. The occurrence of secondary agammaglobulinemia in sprue has not previously been noted but no adequate electrophoretic study of the serum proteins in sprue is available.

The recurrent diarrhea in one of the patients described by Wall and Saislaw [16] was neither febrile nor sprue-like, and no explanation of the relationship of the agammaglobulinemia to the enteric symptoms was ventured.

In Rosecan's [15] patient a fulminating diarrhea developed with weight loss, flat oral glucose tolerance and vitamin A tolerance curves, normochromic anemia, low plasma carotene and azotorrhea. Friable mucosa and rectal ulceration were revealed by sigmoidoscopic examination, and roentgenograms of the small intestine showed segmental narrowing, distorted mucosal pattern and "string signs" in the jejunum. A diagnosis of diffuse jejuno-ileitis related to an altered response to infection was made.

Laboratory Findings. While a diagnosis of agammaglobulinemia may be tentatively advanced on the basis of the typical clinical features, definitive diagnosis requires demonstration that gamma globulin is absent from the serum, or nearly so. The concentration of gamma

globulin in normal serum ranges from 600 to 1,200 mg. per cent, and depression of the level to 150 mg. per cent or less establishes the diagnosis of agammaglobulinemia [17].

Several technics are available to estimate the quantity of gamma globulin present in serum but only two, electrophoresis and immunochemical determinations, are satisfactorily quantitative. Other tests are useful as rapid screening procedures and permit a presumptive diagnosis of agammaglobulinemia.

Electrophoresis of serum proteins by the method of paper chromatography has largely supplanted the more complex and expensive Tiselius moving boundary electrophoresis, although there has been debate as to which method is more accurate in detecting small amounts of gamma globulin. The very precise measurement of gamma globulin levels by immunochemical technic has demonstrated that electrophoresis, whether by the moving boundary, paper, starch or agar method, has a minimum error of 1 to 2 per cent, equivalent, in the case of gamma globulin, to 60 to 120 mg. of protein [17]. The accuracy of electrophoretic measurement has, nevertheless, proved satisfactory for clinical diagnostic work. The unresolved technical problems, such as albumin trailing, protein absorption on filter paper and non-stoichiometric dye absorption, which are obstacles to precise quantitation by paper chromatography, do not vitiate the fact that an absent gamma band means agammaglobulinemia.

Immunochemical Quantitation. Precisely quantitative measurements of minute quantities of gamma globulin employ horse and rabbit anti-human gamma globulin serum. The tests are based on measurement of the distance which a band of precipitate, consisting of gamma globulin plus the antiserum, migrates through an agar medium in a given time. Gitlin, who has performed immunochemical studies in many of the published cases of agammaglobulinemia, has demonstrated that the gamma globulin deficiency is neither absolute nor isolated. He found that serum from patients with primary agammaglobulinemia contained small amounts of gamma globulin, usually less than 25 mg. per cent in the congenital form and less than 100 mg. per cent in the acquired form [18]. More recently he has shown that these patients lack not only gamma globulin but also certain immunoglobulins which electrophoretically migrate as beta globulins [18].

Salting-out Methods. The total protein, albumin and globulin determination, employing the sodium sulfate salting-out technic, is the most widely available screening test for agammaglobulinemia. A globulin value of less than 1.0 gm. per cent is highly suggestive of agammaglobulinemia, since the gamma fraction alone accounts for at least 0.6 gm. per cent in normal subjects.

Back-typing. The serum of the usual patient with agammaglobulinemia has been found to lack isohemagglutinins. Adding his serum to "mismatched" red cells results in no agglutination. Moreover, deliberate challenge with mismatched erythrocytes administered subcutaneously, intramuscularly or intravenously does not evoke a rise in the agglutinin titer such as occurs normally [8]. Back-typing is a simple screening test but it has limitations in that isohemagglutinins may be absent when gamma globulin is present and, conversely, agammaglobulinemia may be present even when isohemagglutinins are demonstrable [19]. The test is, of course, of no value in a patient with blood group AB whose serum is by definition free of agglutinins for group A or B erythrocytes.

Kunkel Zinc Turbidity Test. This procedure, which has been widely used as a "liver function test," is in reality a simple titration for gamma globulin. The values for normal serum range from 2 to 13 units, whereas agammaglobulinemic serum will almost uniformly give a zero reading, or at most 1 or 2 units [8]. The value of this test is enhanced by the fact that most patients suffering from repeated or chronic infection show a definite elevation of the zinc turbidity reaction.

Coombs' Test Inhibition. In 1949 Weiner demonstrated that normal human gamma globulin will inhibit the agglutination which occurs when human erythrocytes coated with antibody (Rh antibody or auto-antibody) are brought into contact with antihuman globulin serum prepared in rabbits. Such inhibition of the Coombs' test would not be expected to occur if serum lacking gamma globulin were employed. Weiner [20] verified this prediction in 1955 in two patients with primary agammaglobulinemia, and in two patients with agammaglobulinemia secondary to multiple myeloma. By means of a serial dilution technic a rough quantitation of the gamma globulin present can be achieved.

The exhaustive studies of Good and Varco [8] in a group of patients with primary agammaglobulinemia have delineated other interesting

features of this syndrome. A large battery of liver function tests was normal. Comprehensive study of the factors involved in blood coagulation revealed no deficiency. Immunologic studies, including Schick and Dick tests before and after immunization, determination of antistreptolysin titer, streptococcal antihyaluronidase, streptococcal antidesoxyribonuclease, heterophil and cold agglutinins, febrile agglutinins (typhoid O and H, paratyphoid B, proteus OX2, OX19, brucella and tularemia), mumps complement fixation, herpes neutralization and poliomyelitis neutralization, showed an absence of these antibodies in all patients. Stimulation with bacterial, rickettsial and viral antigens resulted in no detectable antibody formation. Skin tests with a large number of bacterial antigens gave negative results with the exception of a few equivocal reactions (erythema without induration) in response to P.P.D. Good and Varco concluded that these patients had difficulty in developing delayed bacterial hypersensitivity. However, Seltzer's [21] patient had a repeatedly positive histoplasmin skin test, and Porter [22] induced tuberculin positivity with BCG vaccination in an agammaglobulinemic child who had the remarkably low level of 10 mg. per cent gamma globulin in the serum. He believed that there is an exact immunologic schism in congenital agammaglobulinemia: the body lacks only the ability to produce circulating gamma globulin antibodies.

Although acute phase reactants such as elevations in the erythrocyte sedimentation rate, serum mucoprotein and C-reactive protein may develop in patients with agammaglobulinemia [8], many observers have noted that these patients usually fail to respond to infection with an elevation in the sedimentation rate. Most agammaglobulinemic patients demonstrate such hyporeactivity sporadically, as our patient did, but a few do so with every infection, evincing a permanent incapacity to respond [1,23].

That the erythrocyte sedimentation rate does not rise during acute infection is an arresting feature of agammaglobulinemia. This paradox has both clinical value in suggesting the diagnosis, and heuristic value in the study of mechanisms underlying erythrocyte sedimentation. Elevations in the sedimentation rate have been correlated in previous studies chiefly with rises in fibrinogen and alpha globulin [24], although on occasion a rise in any of the electrophoretically separable globulin fractions may give rise to a

considerably increased sedimentation rate [25]. Gamma globulin is the least effective serum protein in causing elevation of the sedimentation rate [26].

The inference which might be drawn from the fixity of the sedimentation rate in agammaglobulinemia, that normal gamma globulin is perhaps a prerequisite for responsiveness in the sedimentation rate, is controverted by certain observations in patients with multiple myeloma. Very high sedimentation rates are encountered in patients with myeloma who may have very low levels of true gamma globulin. Our studies [27] suggest that elevation of the sedimentation rate in patients with myeloma is due to factors other than the absence of gamma globulin. The transfusion of blood from an agammaglobulinemic patient to a patient with widespread myelomatosis resulted in dramatic falls in the sedimentation rate, which were later duplicated by transfusion with normal blood.

The role of serum complement in the syndrome of agammaglobulinemia is not clear. Kabat et al. [28] demonstrated that normal serum gamma globulin has anticomplementary activity. One would expect increased activity of complement in serum devoid of gamma globulin. This occurred in our patient, as estimated by titrating her serum for complement activity, employing the procedure followed with serum from guinea pigs prior to carrying out complement fixation tests. However, Good and Varco [8] found serum complement normal in six agammaglobulinemic patients, using the method of Wedgewood and Janeway. Kurtz [29] has found slightly decreased levels of serum complement in agammaglobulinemic children, and a high normal value (45 units) in our patient (normal range: 25 to 45 units, 50 per cent hemolytic units).

Hematologic relationships in agammaglobulinemia are especially abundant and intriguing. Leukopenia in the face of major infections is common. Long-term studies have shown that agammaglobulinemic patients may have transient, permanent or cyclic neutropenia [8]. Several observers have noted lymphopenia, and Young et al. [30] have especially emphasized the role of the lymphocyte in agammaglobulinemia by classifying the syndrome into two types, lymphopenic and non-lymphopenic agammaglobulinemia. This emphasis stems from the long-standing controversy as to whether the lymphocyte or the plasma cell is the source of

immunoglobulins. There is weighty evidence on both sides of the argument, and there is now a tendency to accept both cells, and possibly a stem cell common to both, as intimately implicated in gamma globulin synthesis [37].

The lymphatic system displays aberrant behavior in other ways in agammaglobulinemia. Lymph nodes draining areas which have been injected with antigen show proliferation and increased germinal center activity in normal subjects but not in patients with agammaglobulinemia [32]. Lymphadenopathy is common in agammaglobulinemic patients and splenomegaly is almost the rule. Although the splenic enlargement is slight to moderate in most cases, it may become a clinically dominant feature, with hypersplenism. The patient described by Prasad and Koza [23], and later by Zinneman et al. [6] had splenomegaly with non-hemolytic anemia, thrombocytopenia and neutropenia. These abnormalities disappeared following splenectomy, and the leukocytic response to infection became more adequate. A histologic diagnosis of probable Boeck's sarcoid was made from the splenic tissue and from a biopsy specimen of the liver. A hypersplenic mechanism was also corrected in Rohn's [33] patient by splenectomy. In Rosecan's [75] patient, whose spleen extended 11 cm. below the costal margin, the granulocytopenia became temporarily worse following radiation of the spleen. Regression in size of the spleen also proved to be transient.

Thymomas have been described in three patients with agammaglobulinemia, verified in two instances by thoracotomy. Good's [8] patient had an associated absence of eosinophils from the blood and bone marrow. The bone marrow of Ramos' [34] patient with agammaglobulinemia and thymoma showed not only an absence of plasma cells but erythroblastic aplasia as well.

Plasma cells are consistently and conspicuously absent from the bone marrow of agammaglobulinemic patients. Biopsy specimens of lymph nodes and autopsy material have shown that plasma cells are also absent from the lymphatic tissues in these patients. Furthermore, plasma cell proliferation, which normally occurs in bone marrow and in lymph nodes after antigenic stimulation, fails to occur in patients with agammaglobulinemia [32]. The plasma cell defect in agammaglobulinemia is more striking and consistent than the aberrations involving the granulocytes and lymphocytes.

Of profound interest in connection with the

relationship of agammaglobulinemia to plasma cell deficiency is the group of children described by Janeway et al. [35] who had abnormally high levels of gamma globulin, ranging from 1.5 to nearly 6 gm. per cent, associated with unusual predominance of plasma cells in multiple tissues obtained by biopsy and autopsy. Paradoxically, these patients were unusually susceptible to infection, and were originally suspected of having agammaglobulinemia. The electrophoretically "gamma" globulin in these patients would appear to be qualitatively defective from the standpoint of immunity, and the similarities of this pediatric syndrome to certain forms of myelomatosis as seen in adults bear more than passing notice.

TREATMENT

Human serum gamma globulin successfully prevented infection in Bruton's patient after sulfonamide prophylaxis had failed [2]. A dose of 0.1 gm. of gamma globulin per kilogram of body weight intramuscularly every thirty days has given adequate protection to most agammaglobulinemic patients. This dosage is based on two observations: (1) the half-life of injected gamma globulin in humans ranges between thirteen and thirty days [36], and (2) a level of 100 to 150 mg. of gamma globulin per 100 cc. of serum seems to be the minimum necessary to prevent infection [17], a level which is easily obtained by injection of 0.1 gm. per kilogram of body weight. Martin [5] has recently emphasized that gamma globulin is a heterogeneous substance containing many different antibodies which have widely varying half-lives (ranging from seventeen to fifty-eight days), and in an occasional patient larger or more frequent doses of gamma globulin may be necessary.

How long replacement therapy with gamma globulin must be continued is at present unknown. Some patients have had monthly injections for over three years, and there is as yet no report of a patient with primary agammaglobulinemia resuming the manufacture of his own gamma globulin. In certain of the secondary agammaglobulinemias (nephrotic, nutritional, dysproteinemic) resumption of gamma globulin synthesis can be expected to accompany recovery from the primary disorder. Continuous replacement therapy with gamma globulin presents an economic problem, since a patient weighing 70 kg. (154 pounds) would require 7 gm. of gamma globulin monthly. In terms of the

available commercial preparations containing 16 per cent gamma globulin, the required dose of 44 cc. would cost \$132.00.

Although gamma globulin is spectacularly effective in interrupting the fearful chain of infections in most agammaglobulinemic patients, it may occasionally fail. One of three patients described by Hayles et al. [37] died of infection (meningitis, myocarditis and myositis) despite regular administration of gamma globulin. Pneumonia recurred twice during a six-month period of gamma globulin administration in a patient reported by Zinneman et al. [6], and freedom from infection was subsequently provided by prophylactic administration of tetracycline. Zbar's [14] patient received no gamma globulin because of the cost involved, and remained free of significant infection for more than twenty months on oral tetracycline. Martin's [5] patient required sulfadiazine plus double the usual frequency of gamma globulin injections for complete protection (0.1 gm. per kilogram of body weight every fourteen days). Similar combined prophylaxis is now under trial in our patient.

PHYSIOLOGIC AGAMMAGLOBULINEMIA

Infants are born with a level of serum gamma globulin identical with that in the maternal circulation. There follows a gradual decline in serum gamma globulin to very low levels at the age of two to three months, resulting in a physiologic hypogammaglobulinemia. This decline has the characteristics of a simple exponential decay [38], indicating that the newborn child has no ability to manufacture gamma globulin in the early weeks of life. After the third month there is a gradual rise, adult concentrations of gamma globulin being attained at approximately two years of age. Accurate delineation of this curve of gamma globulin concentrations in infancy has shed fresh light on the older clinical observations that immunization procedures are generally futile in infants less than three months of age, and that infections in early infancy may prove fatal in a matter of hours. Physiologic hypogammaglobulinemia has been implicated [39] as an important factor in the causation of so-called "crib deaths."

SECONDARY AGAMMAGLOBULINEMIA

Pronounced depression of the concentration of gamma globulin in the serum may accompany a variety of conditions in which unusual suscepti-

bility to infection may or may not be a clinical feature. In certain patients with simultaneous depression of all the serum proteins, pan-hypoproteinemia, gamma globulin may virtually disappear from the serum. There are several varieties of what may be termed "hypoproteinemic agammaglobulinemia."

In 1945 Schick [40] described a girl who had had edema and hypoproteinemia since infancy. The serum albumin was 3.3 gm. per cent and globulin 0.8 gm., with no gamma fraction on electrophoresis. Exhaustive studies disclosed no hepatic, renal or hematopoietic disease. A report on this patient in 1952 [3], when she was twenty years of age, revealed that she still had edema, hypoproteinemia and agammaglobulinemia. Enigmatically, this patient has been singularly free of infection all her life—this in spite of the fact that no measurable antibody developed following injection of diphtheria toxoid, typhoid vaccine and pertussis vaccine. Her only disability, it seemed, was a psychologic handicap resulting from her "piano legs."

Similar but temporary absence of gamma globulin has recently been described in infants afflicted with "transient dysproteinemia." In this new syndrome pallor, edema and irritability are the chief clinical features. Laboratory studies disclose only an iron deficiency anemia and pan-hypoproteinemia, with no evidence of hepatic or renal impairment. The basic defect appears to be excessively rapid degradation of all serum protein fractions except fibrinogen. Depression of serum gamma globulin in these patients to a level below electrophoretic measurability is apparently devoid of immunologic significance. They exhibit no increased susceptibility to infection, and antibody formation can be successfully elicited by administration of bacterial toxoid. Although anemia is a key feature of the syndrome, bone marrow smears reveal normal conditions, including a normal number of plasma cells, a point of fundamental importance in differentiation from primary agammaglobulinemia. The cases reported earlier by Fried and Henley [42], and by Wyngaarden et al. [43] probably belong in the category of transient dysproteinemia.

The hypoproteinemia of nephrosis involves depression of all the protein fractions with the exception of beta globulin. This secondary agammaglobulinemia is commonly invoked as an explanation for the unusual susceptibility of nephrotic patients to pneumococcal infections.

In most cases of chronic hepatic disease there is a rise in serum globulin concentration but in rare instances hepatic failure may result in gamma globulin deficiency. Thompson et al. [44] described a child with edema from the age of thirteen months until death from pneumonia at the age of two and one-half years. At autopsy the liver showed atrophy of the hepatic cords in the peripheral and intermediate zones of the lobules. The serum globulin in this case fell to as low as 1 gm. per cent and the near absence of the gamma fraction can reasonably be assumed, although electrophoresis was not done.

Agammaglobulinemia may rarely arise on the basis of malnutrition. Krebs [45] described electrophoretic absence of gamma globulin from the serum of a patient whose proteins were severely depleted (3.1 gm. per cent, total) on the basis of starvation. Administration of typhoid vaccine failed to elicit antibody formation. The serum proteins including the gamma fraction were restored to normal by a nutritious diet.

Agammaglobulinemia may occur as a feature of several neoplastic diseases. Very high values for globulin are often encountered in multiple myeloma, using the standard sodium sulfate salting-out technic, and a large peak is often seen in the gamma region during electrophoresis of myeloma serum. These observations tend to obscure the fact that patients with myeloma may actually have no normal gamma globulin. The abnormal globulin in a patient with myeloma may migrate with the speed of alpha (rarely), beta or gamma globulin, or at a speed intermediate between beta and gamma ("M-protein"), or backward from the starting point, so-called "gamma S." It is particularly when myeloma globulin migrates in the vicinity of the gamma zone that the absence of true gamma globulin will be overlooked. This occurred in the following patient who had asymptomatic secondary agammaglobulinemia.

CASE II. A forty-six year old housewife was admitted to the hospital on August 1, 1955, complaining of pain in the lower back and in the legs of two months' duration. Concomitantly frontal headaches and postural dizziness had developed. Physical examination was within normal limits except for mild pallor and slight tenderness to percussion over the lumbar area. Urinalysis showed 1 plus albumin and rare hyaline casts. The erythrocyte count was 3,650,000 per cu. mm.; hemoglobin, 9.7 gm. per cent; and the erythrocyte sedimentation rate, 137 mm./hr. The serum albumin was 2.8 gm. per cent and globulin,

6.8 gm. per cent. In smears of sternal marrow 40 per cent of the nucleated cells were plasmacytes. A serum protein electrophoresis was reported to show a very high gamma globulin value. Repeat electrophoresis with a normal serum in parallel demonstrated that the dense band actually represented M-protein. (Fig. 1.)

This patient has survived eighteen months since the onset of her disease, and six months since the absence of gamma globulin was demonstrated. During the period she has had only one infection, a mild cystitis.

Contrary to our experience in Case II, the absence of normal gamma globulin in patients with myeloma is often expressed clinically by remarkable susceptibility to infection. Zinneman and Hall [46] cited thirty-four episodes of pneumonia in their series of ten patients with myeloma. Stimulation with bacterial antigens resulted in practically no antibody response in their patients. The immunoglobulin defect is probably not complete in myeloma, since isohemagglutinins are present. Porges [47] has recently called attention to the fact that serum electrophoresis is a simple method for simultaneously arriving at two diagnoses—multiple myeloma and secondary agammaglobulinemia. Two of his patients with myeloma had a history of recurrent major infections.

Arends et al. [48] described a patient with malignant lymphoma who had to be hospitalized repeatedly with respiratory and cutaneous infections. The serum contained no gamma globulin and no plasma cells could be identified in the bone marrow. Brem and Morton [49] reported two cases of chronic lymphatic leukemia with secondary agammaglobulinemia. One patient with the very rare syndrome of erythroblastic hypoplasia accompanying a thymic tumor [34] was found to have agammaglobulinemia. This patient was prone to diarrhea and skin infections. Thymic tumors were also encountered in Martin's [5] and in Good's [8] patients; in the latter a benign thymoma was surgically removed. Both of these patients were reported originally as instances of primary agammaglobulinemia, and the thymic enlargement could perhaps be construed as a secondary phenomenon similar to the lymphadenopathy and splenomegaly so common in agammaglobulinemic patients.

It is of considerable interest that the only neoplastic diseases with which agammaglobulinemia

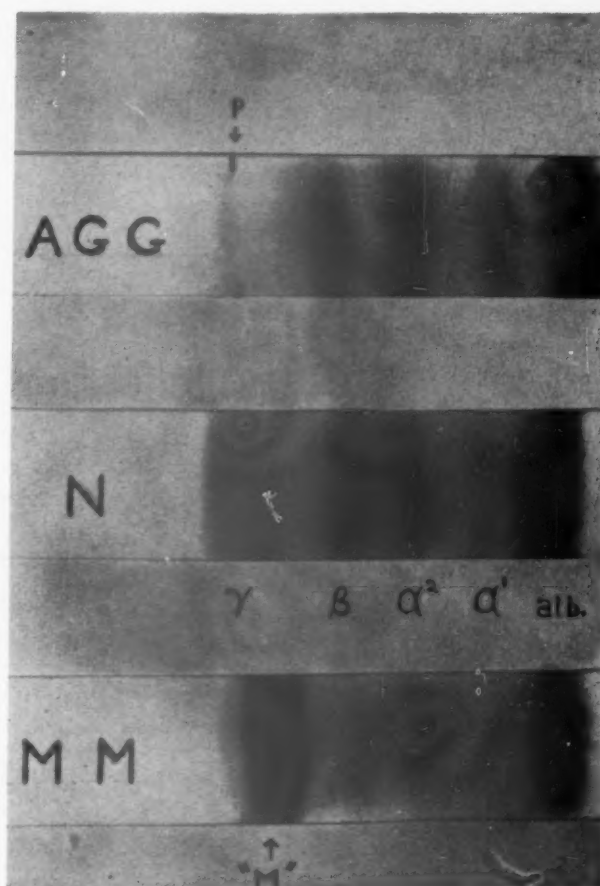


FIG. 1. Serum protein electrophoretograms from a patient with agammaglobulinemia (AGG), a normal subject (N) and a patient with multiple myeloma (MM). Point of application of serum to filter paper indicated by P. Absence of gamma band in AGG is demonstrated. M-protein is seen to migrate in zone between normal beta and gamma.

has been found to be associated are those originating in the hematopoietic system. More specifically, secondary agammaglobulinemia is confined to neoplasms of the lymphocyte-plasmacyte series of cells: lymphoma, lymphatic leukemia and multiple myeloma. Agammaglobulinemia has not, for instance, been found in association with myelogenous leukemia. This highly selective association might be interpreted as additional evidence that gamma globulin originates in lymphocytes and/or plasma cells. The mechanism by which malignant transformation of lymphocytes or plasma cells results, in certain instances at least, in a loss of ability to synthesize gamma globulin is not immediately clear. Loss of immunoglobulin-synthesizing capacity may simply represent the loss of specialized function which characterizes the neoplastic cell.

IMPLICATIONS

Good [8] has pointed out that agammaglobulinemia is a "provocative experiment of nature," the duplication of which could be enormously fruitful. The potential usefulness of artificially induced agammaglobulinemia is perhaps greatest in the field of homologous tissue transplantation. Recent reports of successful transplantation of kidneys in identical twins, with great benefit to the recipient, have given new impetus to the quest for a method of universal homologous grafting. Homologous skin grafts which are used as a temporary cover in extensive burn cases invariably slough within six to eight weeks. Subsequent homologous grafts are rejected even more quickly. Rejection is thought to be due to an antigen-antibody reaction. Since agammaglobulinemic patients are unable to form antibody, homologous grafting is theoretically feasible. Good has described a child with primary agammaglobulinemia who has had a successful homologous skin graft remain intact for eight months [8].* Successful homotransplantation of normal lymph nodes into patients with agammaglobulinemia has resulted in restoration of the ability to manufacture antibody, as demonstrated by challenge with typhoid-paratyphoid vaccine [5,7].

Another implication of "nature's experiment" arises from the contrast between primary agammaglobulinemia and multiple myeloma. In the former, gamma globulin and plasma cells are conspicuous by their absence, while in the latter there is unbridled proliferation of plasma cells with elaboration of large quantities of serum globulin. The cause of the ablation or suppression of plasma cells in agammaglobulinemic patients is, of course, unknown. If it were due to some single discoverable factor, such as a protein circulating in the serum, the use of such a "plasmacytostatic factor" might have therapeutic implications in the management of multiple myeloma. Our preliminary investigations [27] of this possibility have shown no clearcut morphologic changes in plasma cells from a patient with myeloma which were incubated with agammaglobulinemic serum. Serial bone marrow studies following transfusion with agammaglobulinemic blood failed to show any definite effect on the neoplastic plasma cells.

* This graft has now been in place for almost three years; a similar graft in another child has survived over two years. (Good, R. A. Personal communication.)

Elevation of the serum globulin concentration occurs with appreciable regularity in many infectious and in inflammatory diseases [50]. Such elevations are usually due to alpha globulin but concomitant elevations in gamma globulin are frequent and become more conspicuous with increasing chronicity of the infection. In these circumstances, gamma globulin increase reflects a normal immunologic response to the invading agent.

In certain conditions, such as rheumatic fever and acute glomerulonephritis, the immune response to infection is thought to be responsible to a large degree for the pathogenesis of disease. Exaggerated immune response is implicated to an even greater degree in the pathogenesis of other members of the collagen disease family, particularly periarteritis nodosa and systemic lupus erythematosus. In the latter disease, the serum factor responsible for production of the characteristic L.E. cell has been shown to be a gamma globulin [51]. In these conditions an ability to thwart the hyperergic response by inhibiting production of noxious gamma globulins might provide a new therapeutic approach.

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Seminar on Atherosclerosis

Nutritional Factors and Serum Lipid Levels*

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THE correlation between the amount of dietary fat, the concentration of serum cholesterol and the incidence of ischemic heart disease† is widely accepted as a cause and effect relationship by nutritionists, public health authorities, biochemists, practising physicians and by the public itself. Evidence favoring this correlation has been presented in a large number of epidemiologic studies, among which those of Keys et al. [2,3] figure prominently. The validity of the conclusions drawn from these data has been questioned on numerous occasions, most recently by Yudkin [4], Yerushalmy and Hilleboe [5] and Mann [6].

Their warning bears repetition: a direct correlation, no matter how strong, cannot be used as proof of cause and effect. Each of these reports has emphasized the weaknesses inherent in the basic data, in the mortality statistics, in the food consumption data and in the statistical treatment applied to the data. Their evaluations do *not* indicate that dietary fat has nothing to do with the incidence of ischemic heart disease; they *do* emphasize that conclusive proof of a specific association is still lacking. Indeed, the correlations between ischemic heart disease and the intake of animal protein or sugar, the number of television sets or automobile licenses, are said to be stronger than those with total fat, animal fat, vegetable fat, butter fat or margarine. Other defects in the postulate that ischemic heart disease is caused by eating too much fat (or too

much of certain kinds of fat) have been pointed out by Page [7] and by Ahrens [8] and their colleagues.

Whether this postulate eventually is proved correct or not, it can be said without fear of question that our knowledge of the factors which control serum lipid levels, although still fragmentary, has grown enormously in the last ten years. It is the purpose of this report to summarize current concepts on this subject, on the grounds that a sound basis of understanding of fat metabolism underlies a true evaluation of its role in arteriosclerosis. In 1951 Davidson [9] discussed the effect of lipotropic agents on serum lipids and on experimental atherosclerosis. He concluded that there was "no general agreement that choline or inositol have any specific influence upon arteriosclerosis or the serum cholesterol level in man or the experimental animal." With certain exceptions, which will be discussed subsequently, this statement still stands, and we shall say little here about lipotropic agents. Neither can we be concerned here with clinical or experimental studies of atherosclerosis or hypertension except insofar as they contribute to an understanding of the relationship of nutrition and serum lipid levels. Finally, the vistas opened up by the recent work on clearing factor and non-esterified fatty acids in serum are too complex to include here; recent views on these topics can be found in the publications of the Third and Fourth International Congresses on Biochemical Problems of Lipids (Brussels, 1956 and Oxford, 1957, respectively), and the summary by Robinson and French [10]. Other reviews which may prove helpful for study in this field include *Fat Metabolism* [11], edited by Najjar, and *The Chemistry of Lipids As Related to Atherosclerosis* [12], edited by Page. Recent technical developments in lipid biochemistry are described in the three volumes entitled

† "Ischemic heart disease" is the term adopted by the Study Group on Atherosclerosis and Ischemic Heart Disease, World Health Organization, Geneva, November 7, 1955, to denote the "cardiac disability, acute or chronic, arising from reduction or arrest of blood supply to the myocardium in association with disease processes in the coronary arterial system." It includes the processes of atherosclerosis and thrombosis in those vessels, and supplants the less precise but more generally accepted term, "coronary heart disease" [7].

* From The Rockefeller Institute, New York, New York. Supported in part by the U. S. Public Health Service (H-2539), the Williams-Waterman Fund, and the Nutrition Foundation.

Progress in the Chemistry of Fats and Other Lipids, edited by Holman, Lundberg and Malkin [13]. The encyclopedic reviews of lipid biochemistry by Hilditch [14] and Deuel [15] are essential references, and the small text by Lovern [16] is condensed but highly informative.

This review will include a consideration of calories *per se* and of total energy balance in relation to serum lipid levels. Dietary fats, protein and carbohydrate will be separately considered, then intestinal bacteria, "bulk" and, finally, trace substances. Current views on fat digestion and absorption cannot be included here; a recent review of this subject by Bergström and Borgström [17] may be of interest.

GENERAL CONSIDERATIONS

Although the major part of this review discusses the effects on serum lipids of the major foodstuffs—fat, protein and carbohydrate—a consideration of any one falls out of context unless total energy balance is considered simultaneously. It is not enough to speak of fat intake, either in grams per day or as a percentage of total calories; one must also relate this intake to total body needs. Does the day's diet contain more than, less than, or just enough calories to maintain body weight constant? For simplification we will assume constant physical activity and a fixed metabolic state unaffected by disease, fluctuating hormonal balances or needs for growth.

We must deal with a four component system—total calories, fat calories, protein calories and carbohydrate calories—in which the first is the sum of the other three. For graphic purposes it may be helpful to plot the interrelationships on a triangular phase diagram (Fig. 1) in which the corners of the equilateral triangle represent 100 per cent of the individual caloric sources. The bases opposite each corner represent 0 per cent, and lines drawn parallel to each base define various degrees between 0 and 100 per cent for each component. It is a matter of simple geometry to show that any point within the triangle exactly defines the total dietary mixture; the sum of the three values represented by each point adds to 100.

Within the limits imposed by the availability of foods and by human ingenuity in preparing them and tolerance in accepting them, the human diet might be defined by a point anywhere within the triangle. However, it is already well known that certain minimum requirements

for dietary protein must be met if the diet is to be satisfactory over long periods of time. The exact position of this minimum has not yet been established [18], but it is safe to state that under ordinary circumstances the adult human being can thrive if he receives at least 8 per cent of his

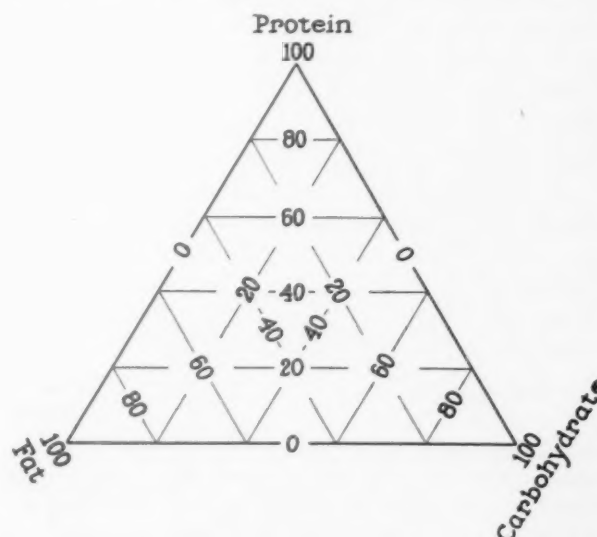


FIG. 1. Diagrammatic representation of diet composition, in which angles represent 100 per cent of the three major foodstuffs, while the sides opposite each angle represent 0 per cent. The three values depicted by any point within the triangle add up to 100.

calories as mixed vegetable and animal proteins of good quality. (Probably, this minimum limit is considerably lower.) A line drawn parallel to the base opposite "protein" at 8 per cent defines this limit. Now, excepting the Eskimo (whose dietary intake has never been adequately defined), the protein intakes of a wide variety of the world's peoples lies between 8 and 15 per cent of total calories [5,19]. Thus, we may think of another line parallel to the protein base at 15 per cent, which defines the maximum protein intake ordinarily eaten.

When natural protein intakes vary over a twofold range from 8 to 15 per cent in various parts of the world, what happens to fat and carbohydrate intakes? Data gathered from the literature by Keys and Anderson [19] have been plotted in Figure 2. It is readily apparent that the Eskimo diets are in a class by themselves. The other data take a linear form: as protein intakes slowly increase, there is a major replacement of carbohydrate by fat calories. Thus, from one extreme to the other, there is a difference of only 5 per cent of calories as protein, whereas fat calories increase from 10 to 45 per

cent at the expense of carbohydrate. The diets of civilized countries like the United States are found at the left, while the diets of underprivileged areas are at the right. We may ask why these points are not scattered randomly over the entire chart. Is it a matter only of

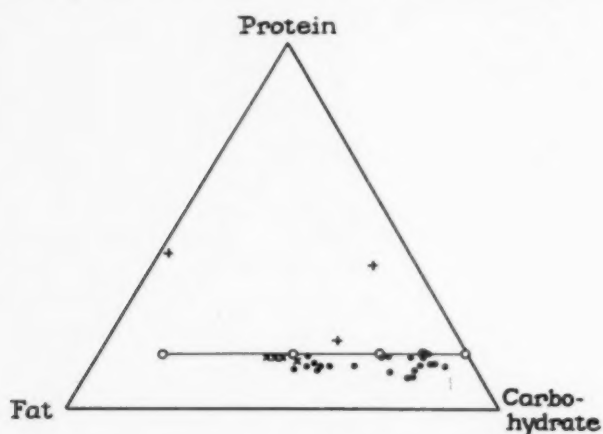


FIG. 2. Dietary compositions of (•) naturally selected diets eaten by various peoples; (X) = diets in the United States; (+) = diets of Eskimos, from data listed by Keys and Anderson [19]. Dietary compositions tested by Ahrens et al. [62] also shown: ○—○.

palatability and appetite [20]? Economic considerations and the inherent constitution of readily available foods must also play an important part in determining the composition of naturally selected diets. Whatever the reasons, the data in Figure 2 distribute themselves in a more or less orderly progression. Since this is so, any correlation between an event (like ischemic heart disease) and any *one* food component must by definition imply a correlation with the other two. Thus, if the incidence of ischemic heart disease actually were correlated strongly with total fat intake, it must also be correlated inversely with carbohydrate intake. The student of disease is still left with the question, is the event meaningfully related to the excess of one element or to the deficit of the other element, or is the entire association fortuitous?

This graphing method has the disadvantage of hiding the facts that (1) proteins vary greatly in their food value, (2) fats of different chemical structures seem to have different metabolic roles, and (3) starches are not always equivalent to simple sugars. These differences will be discussed in detail later. The graph does illustrate the dilemma of the investigator who wishes to explore some effect of one or another class of food calories. Clearly, he cannot add or subtract one foodstuff without altering both the

composition of the dietary mixture and the total energy balance. The investigator who asks whether dietary fat affects serum lipid levels must decide whether or not to make reciprocal changes in carbohydrate intake, in which case the effect produced may be due either to the smaller intake of one component or to the larger intake of the other, or to both. Or he may add or subtract fat calories without changing protein and carbohydrate intakes, in which case the effects observed may be due to the change in fat, to the altered energy balance or to the altered food mixture.

The importance of these considerations can be illustrated by two examples. (1) A study by Messinger et al. [21] aimed at learning whether or not an increased cholesterol intake would cause an increase in serum cholesterol concentrations. The cholesterol intake was increased by feeding egg yolk powder, and a marked increase in serum cholesterol levels was obtained. However, the design of the experiment did not permit a clear answer to the alternate possibilities that this rise was due to the increased cholesterol intake (3.5 gm. per day) or to the increased caloric intake (1,000 calories per day), or to both changes. (2) A recent study by Insull et al. [22] has shown that the fatty acid composition of human breast milk was radically affected by the quantity and quality of the mother's dietary fat. Moreover, it was also altered by feeding more, and later less, calories than were required to maintain her body weight constant. This study clearly demonstrated that the response of the human breast is conditioned by total energy balance as well as by the character and amount of fat in the maternal diet. These important interrelationships are frequently overlooked in the design of metabolic experiments in animals as well as in man.

TOTAL CALORIES

This section deals with the effects on serum lipid levels of over- and undernutrition, that is, more or less calories than are required to maintain constant body weight at "normal" levels. This definition, at the outset, begs terms, for we cannot define normal weight nor even describe the state of optimal nutrition. What is normal or optimal for one race need not apply to another. Nor in any one race are these values unaffected by age, sex, body build and many other factors.

Caloric Deficit. The effect on serum lipid levels of prolonged undernutrition has been summarized by Keys et al. [23] in their monograph, *The Biology of Human Starvation*. In addition to reviewing the literature up to 1948 they contributed original data in their experiment on twenty-three normal, young volunteers who were fed 1,700 calories per day (protein, fat, carbohydrate = 13, 18 and 69 per cent of calories) for 128 days. Small but significant decreases in total cholesterol levels were obtained in eighteen of twenty-three men, with mean levels decreasing from 169 to 151 mg. per 100 ml. serum. Total serum lipids were unchanged. There was no ketosis.

Two studies of the effect of weight reduction on serum cholesterol and lipoprotein levels were reported by Walker et al. in 1953 [24] and in 1957 [25]. Both reports indicated that significant decreases in cholesterol and in the high-density beta-lipoproteins can be accomplished under various conditions of (1) rate of weight loss, (2) initial levels during weight maintenance, and (3) composition of the dietary mixture during weight reduction. The studies are not sufficiently controlled to permit precise conclusions to be drawn.

The results of Moore et al. [26,27] suggest that men and women may respond differently to weight reduction regimens.

Changes in serum lipid levels during *total* starvation were described by Kartin et al. [28] in 1944. Men, monkeys and dogs were studied; ketosis and hypercholesteremia failed to develop in dogs only. In man there were significant increases in cholesterol, larger rises in phospholipids and equivocal changes in triglycerides. These changes were reversed by administration of carbohydrate. These workers concluded that the existence of "starvation lipemia" is highly questionable. In 1954 Rubin and Aladjem [29] demonstrated by ultracentrifugation technics that a four to five day fast in six healthy volunteers caused (1) no appearance of $Sf_{>400}$ lipoproteins, and therefore no lipemia, (2) marked increases in Sf_{12-20} and Sf_{20-100} groups, (3) less marked increases in Sf_{0-12} and $Sf_{100-400}$ groups, and (4) no significant change in high-density lipoproteins (<1.125 and 1.199). These changes were readily reversed twenty-four hours after resumption of normal meals. One of the six volunteers who failed to show these changes had been on a low-fat (<15 gm./day) diet for more than two years; his response resembled

that of Kartin's dogs [28] which were acclimated to high carbohydrate diets.

We know of no controlled study of the effects of variously composed diets on serum lipid levels during states of negative energy balance. It seems reasonable to predict that the incorporation of different dietary fats in subcaloric diets may have relatively little specific effect, since the combustion of the semi-starved patient's own adipose tissue comprises a large part of his total energy expenditure. In their study of breast milk fatty acids, Insull et al. [22] showed that during restriction of total calories the fat composition of breast milk closely resembled human adipose tissue in its pattern of fatty acids. It would be of particular interest to examine the closeness of identity of (1) the various groups of esters in the serum, (2) the non-esterified fatty acids in the serum and (3) the adipose tissue fatty acids during periods of weight reduction.

Caloric Excess. The effects of excess calories on serum lipid levels have been even less well defined. There has been no systemic study of variations in fat/carbohydrate calories, although profoundly different effects on the serum lipids might be expected. The study of Walker et al. [24] demonstrated in two men that excess calories over a short period caused striking increases in serum cholesterol and lipoprotein levels, even though the diet was low in fat. In an extension of this project, Mann et al. [30] showed that these increases could be prevented if sufficient exercise were taken to dissipate the excess food calories. In both studies mixed natural diets were fed, and all four parameters—calories, fat, protein and carbohydrate—were simultaneously varied.

In a well controlled metabolic study of twenty physically healthy schizophrenic men, Anderson et al. [31] demonstrated that weight gains due to a daily excess of 660 calories caused significant elevations of total cholesterol (20 mg. per 100 ml. serum). These levels reached their peak at five weeks and were maintained unchanged for fifteen more weeks despite continuing gains in weight. On the other hand, increases in Sf_{12-20} lipoproteins took place from the tenth to twentieth week. (Since initial levels were not reported, it is not known how this class varied in the first ten weeks.) Other lipoprotein groups, triglycerides and phospholipids were not measured, although one might expect significant alterations in these components.

Much attention has been paid by nutritionists to the effects of dietary deficiency. Its counter-

part—dietary excess—has been long neglected. The animal studies of McCay [32], Silberberg [33], Thomasson [34], McCance [35] and others showed that underfed animals live longer than animals fed *ad libitum*. The relative merits of a Sybaritic or a Spartan existence for human beings can be debated, but it is clear that much fundamental information on fat metabolism must be acquired before the issue will rest on facts instead of emotions.

FAT

Prior to World War II Snapper initiated studies of the iodine values of the serum lipids of Occidentals and Orientals in China [36]. He stated in his 1941 text [37] on Chinese medical conditions that "whereas the Westerner depends for his linoleic acid intake on the traces which may be present in some of the ingredients of the diet, the Chinese ingests daily from his early youth considerable amounts of the important unsaturated compounds." He postulated that these differences in diet might be related to the scarcity in China of a number of diseases, among them arteriosclerosis. Regrettably, his efforts were interrupted by the war and were not resumed.

Snapper's idea was based on the demonstration by Burr and Burr [38] in 1929 that linoleic acid was essential for the growth of rats exhibiting a deficiency syndrome characterized by a scaly skin. The earliest attempts to relate essential fatty acid metabolism to clinical disease were made by Hansen and Wiese, colleagues of the Burrs, who considered that infantile eczema might be an expression in man of essential fatty acid deficiency [39]. It has long been known that the feeding of highly unsaturated fats causes a rapid rise in concentration of unsaturated acids in the depot fat of many organisms, but the possibility that the ingestion of fatty acids of certain double-bond structure might affect serum lipid levels had no supporting evidence until 1955, when reports by Kinsell [40] and by Ahrens [41] and their co-workers opened the question. A description of the present status of this problem will form the main part of this section.

For purposes of historical review it is well to remember that, until cholesterol was shown to be synthesized in the body from smaller units by Rittenberg and Schönheimer [42], it was considered that the cholesterol of the diet was the main determinant of serum cholesterol levels.

In fact, when Schönheimer [43] in 1933 placed a hypercholesteremic woman on a plant fat diet, he did so in order to feed a cholesterol-free diet. He demonstrated a striking decrease in her serum cholesterol levels, and his study of her fecal sterols indicated that she either converted her serum cholesterol to some other compound or segregated it in another tissue, for it was not excreted. It is now believed that dietary cholesterol does not affect serum cholesterol levels (*vide seq.*). The changes in serum levels which Schönheimer observed may have been due to the patient's high intake of olive oil and margarine. On the other hand, Sperry and Schick's [44] failure to affect the serum cholesterol concentrations of a child with hypercholesteremia by means of a cholesterol-free diet may have been due to the fact that their diet was almost devoid of fat of any type.

The effects of vegetarian diets were further explored by Hardinge and Stare [45] whose study was initiated in 1950 and reported in 1954, and by Groen et al. [46] whose report appeared in 1952. The former workers demonstrated that strict vegetarians had lower serum cholesterol levels than the partial vegetarians who ate eggs and dairy products, or than non-vegetarians. Groen devised an experiment in which individual responses to three different diets were tested. Serum cholesterol levels were lowest on the vegetarian regimen, even though the total fat intake was high, and were highest on the animal fat diet. While numerous questions remained unanswered, Groen's data demonstrated clearly that serum cholesterol levels *could* be independent of total fat intake.

In 1952 Kinsell et al. [47], investigating the effects of diet on the response in patients to various endocrine preparations, reported that diets high in vegetable fat produced dramatic decreases in serum cholesterol and phospholipid levels, whereas isocaloric substitution of animal fats in these diets caused the levels to rise promptly. They noted that the addition of cholesterol to the vegetable fat diet did not reverse the effect.

The 1952 reports were viewed with some scepticism at the time, because numerous workers had shown that serum cholesterol levels decrease significantly on low fat diets [2,48-53] and that the addition of vegetable fats to these regimens produced a dramatic rebound of cholesterol concentrations to previous levels [54-57]. However, the results of a four-month

study of six patients by Ahrens et al. [58] carried out under metabolic ward conditions with strict isocaloric substitution of mixed animal by mixed vegetable fats and with constant intakes of the same dietary protein, amply confirmed the conclusions of Kinsell, Groen and Hardinge.

In retrospect, it seems probable that some of the confusion between 1952 and 1954 arose because the importance of maintaining food intakes at eucaloric levels was not appreciated. Perhaps, the fetishism associated with the practice of vegetarianism also may have influenced reactions to the early claims. (An illuminating historical review [59] was published by the eminent nutritionist, L. B. Mendel.) But perhaps a greater handicap to clear thinking was created by the standard industrial practice of naming fats "animal" or "vegetable." As later events have shown, this arbitrary division is chemically meaningless and even misleading. The errors in thinking created by this unfortunate custom were in some instances further compounded by failure to distinguish between hydrogenated and non-hydrogenated fats. In addition, the well regarded studies of Keys et al. [7] showed that serum cholesterol levels could be influenced by adding or withdrawing dietary fat but not by altering the intake of dietary cholesterol. Because Keys made no distinction at that time between fats of specific chemical structure, he became convinced that total dietary fat was the key factor determining serum levels of cholesterol. His recent reports indicate that he has modified this position [60].

Recent experiments in a number of laboratories have shown clearly that isocaloric exchanges of different fats in the diet produce an array of serum lipid changes which can be related to the degree of unsaturation of the fed fat. Kinsell [40] and Ahrens [47] originally suggested this explanation of their experiments in 1955. Their later results [8,61-63] and those of Bronte-Stewart [64], Beveridge [65,66], Keys [60,67], Malmros [68], Eggstein and Schettler [69] and their co-workers are at least consistent with this hypothesis. Thus, the ingestion of highly saturated fats (butter, coconut oil, cocoa butter, palm oil, for example) leads to the highest levels of serum cholesterol and phospholipids, while diets containing isocaloric amounts of highly unsaturated oils (safflower, corn, cottonseed and peanut oils, for example) produce striking decreases in these levels. These changes are produced without altering the ratio of free/total

cholesterol, and there is no indication of liver injury or indeed of any other recognized ill effect. Curiously, the concentrations of serum triglycerides are not systematically altered by these dietary fat exchanges. It has been shown [62] that the serum lipid levels produced by a

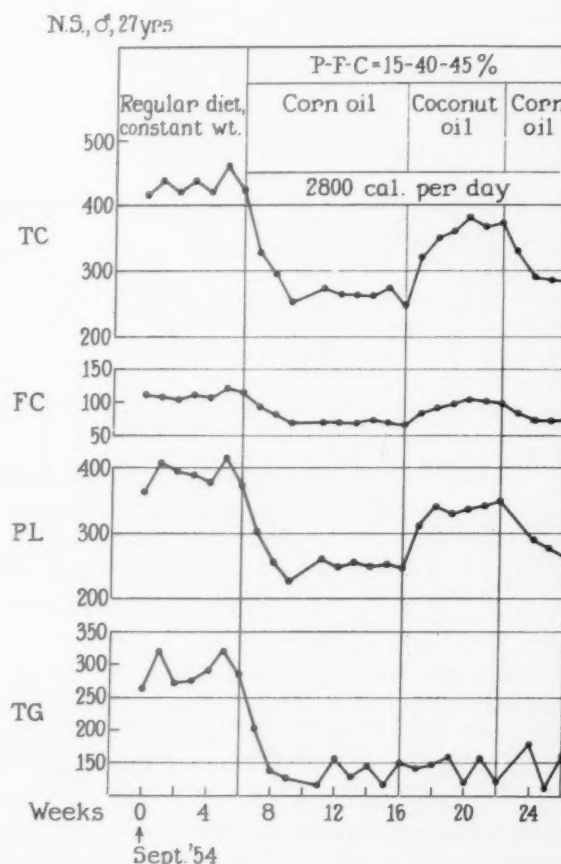


FIG. 3. Twenty-six-week study of serum lipids in a twenty-seven year old man with hypercholesteremia; no apparent vascular disease or xanthomatosis. TC = total cholesterol, FC = free cholesterol, PL = phospholipids, TG = triglycerides, all in mg. per 100 ml. serum. P-F-C = Protein, fat and carbohydrate intakes, as percentage of total calories. Note three-week transition periods after each dietary exchange, before levels became steady.

given dietary fat persist as long as that regimen is continued (the longest experiment we have carried out on an unchanged dietary regimen has been twenty-six weeks). The unsaturation hypothesis is strengthened by the fact that hydrogenation of the unsaturated oils at least partially destroys the effectiveness of those oils in lowering serum cholesterol and phospholipid levels. In addition, if most of the non-fatty acid materials in dietary fats are removed, either chemically or by molecular distillation, the

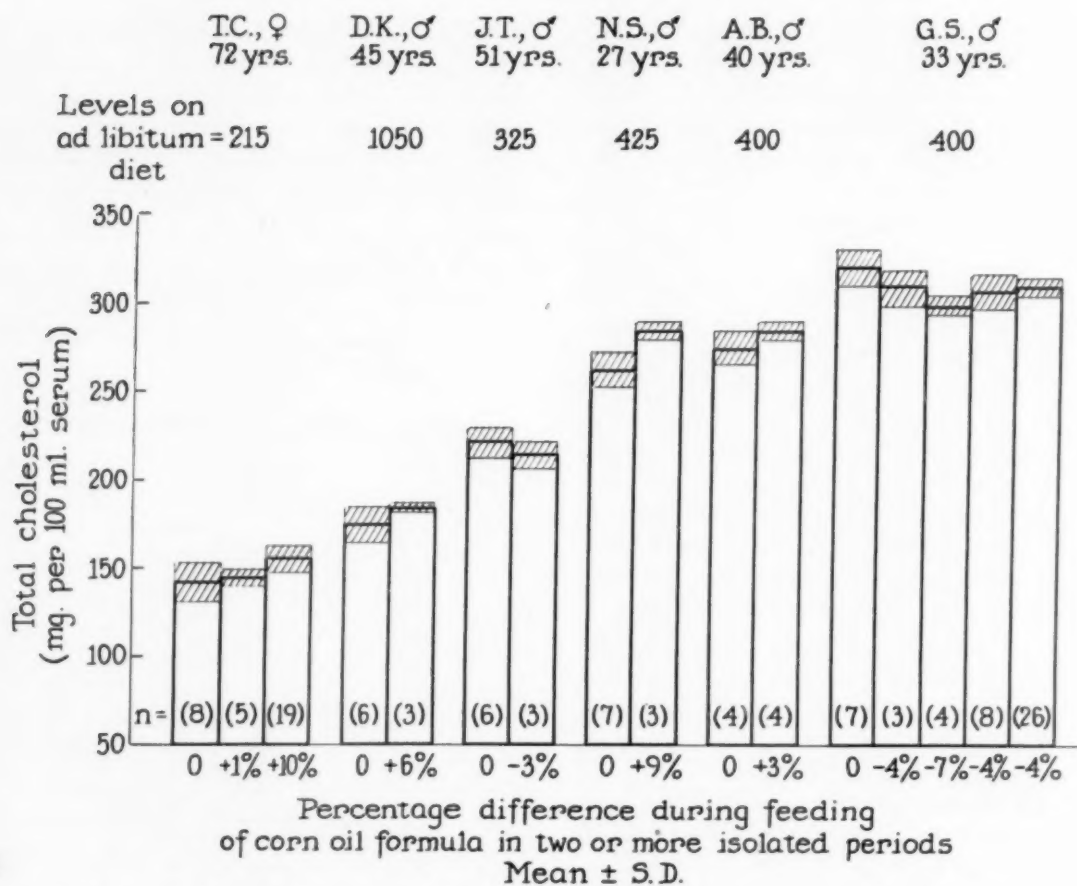


FIG. 4. Reproducibility of serum cholesterol levels in six patients retested on basic corn oil formula (P-F-C = 15 to 40 to 45 per cent of calories), with other regimens in intervening periods. Bars show mean levels during steady states, hatched areas = one standard deviation, n = number of weekly data during each steady state. Percentage differences along baseline calculated with reference to mean levels of first feeding periods.

characteristic response of the patient to that dietary fat is not lost.

Experiments that substantiate these statements are shown in Figures 3 to 7. Figure 3 demonstrates that a saturated fat, coconut oil, causes higher lipid levels than an unsaturated oil, corn oil. When corn oil formula is fed repeatedly to the same patient (other feeding periods intervening), the same cholesterol levels are achieved within ± 5 per cent. (Fig. 4.) As all patients do not respond to corn oil to the same degree, the serum lipid levels achieved during ingestion of the corn oil formula must be used as control values for each patient. The percentage differences between control levels and those produced by other dietary fats can be calculated. When these percentage differences are related to the iodine values of the various fats tested, a linear relationship is obtained. (Fig. 5.) The ingestion of formulas containing corn oils saturated by hydrogenation to iodine values of 80 and 58 produces successfully higher levels of cholesterol

and phospholipids in the serum (Fig. 6), and the removal of 80 per cent of the non-saponifiable materials (such as sitosterols, carotenes and tocopherols) from corn oil failed to abolish its cholesterol-lowering properties. (Fig. 7.)

It is keenly debated today whether the effects described are due (1) to the presence in all natural fats of trace materials, i.e., plant sterols, vitamins, minerals; (2) to the absence in most oils of short and intermediate chain length fatty acids, i.e., the C_{4-14} acids so richly distributed in coconut oil and butter; (3) to the content of essential fatty acids in most natural fats and oils, i.e., linoleic, arachidonic or others; or (4) to the aggregate unsaturation of the oil, i.e., the number of double bonds per unit weight of carbon.

Jones et al. [70] reported experiments in chicks which suggested that the corn germ contains substances more potent than the oil itself as depressants of serum cholesterol levels. Beveridge et al. [71] reported evidence which suggested

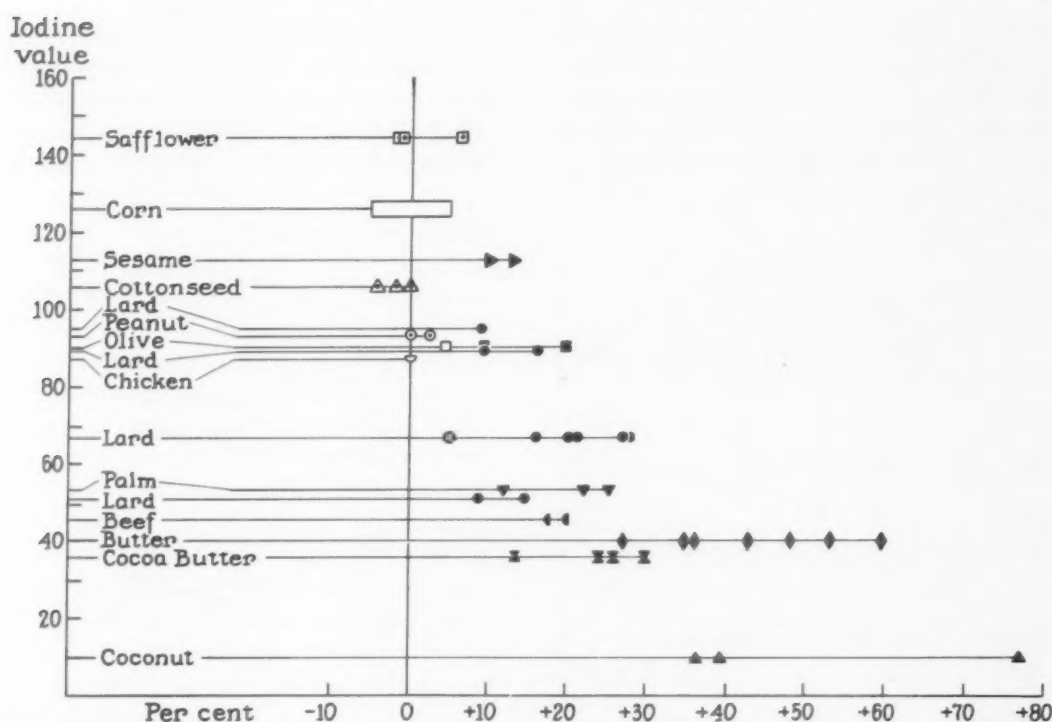


FIG. 5. Relationship between iodine values of dietary fats and serum cholesterol levels expressed as percentage differences from base lines established during ingestion of corn oil. Iodine values of fats listed along vertical axis. Open bar at iodine value 126 = estimated reproducibility of corn oil baseline. (Fig. 4.) Open symbols represent results not significantly different from base line, solid symbols different at level of $p < 0.01$, hatched symbols different at level of $p < 0.05$.

to them that the effectiveness of corn oil is due largely to its beta-sitosterol content. We believe that their data permit other interpretations, but readily agree that the importance of the role played by corn oil's sitosterol must be clarified.

Experiments reported by us [62] suggest that the ingestion of fatty acids shorter than C_{16} may produce higher serum cholesterol and phospholipid levels than the C_{16} and C_{18} acids. Thus butter, which is rich in short and intermediate chain length acids, produces higher serum lipid levels than does cocoa butter, which contains predominantly C_{16} and C_{18} acids, yet these fats contain the same amounts of oleic and linoleic acids. On the other hand, Keys [72] has seen no rise in cholesterol levels after feeding 10 gm. per day of butyric acid.

Kinsell and Sinclair [67] postulated that the major determining factor in the highly unsaturated oils is their content of linoleic acid, and that hypercholesteremia and atherosclerosis are expressions in man of a deficiency of essential fatty acids. These conclusions are weakened by the following considerations: (1) significant depressions in serum cholesterol, phospholipid and beta-lipoprotein levels have been produced

by ingestion of sardine oil [67], whale oil [68] and pilchard oil [64], although the analytical data currently available [73] indicate that these oils are exceedingly poor in essential fatty acids, and rich in other unsaturated fatty acids; and (2) serum lipid levels have also been depressed by feedings of olive oil [62,68] and rapeseed oil [68] which consist mainly of mono-unsaturated "non-essential" fatty acids, and by linseed oil [69] rich in tri-unsaturated non-essential linolenic acid. These considerations lead us to the tentative conclusion that the major factor in dietary fats which produces depressions in levels of cholesterol and phospholipids in the serum is the total mean unsaturation of the fat, that is, its number of double bonds. We disagree with Keys et al. [60] in their statement that mono-unsaturated acids are neutral in effect and have shown elsewhere [63] what we consider to be the fallacy of their arithmetic.

In the last analysis, all these currently debated issues will be settled by adequately designed experiments. We have stated [63] why we believe that future experiments must lean heavily on the use of "synthetic" fats, in which the experimenter has more flexible control of the fatty acid

composition of dietary fat than Nature allows him. It is indeed unfortunate that species differences demand that such experiments be performed in the human being, for this path is thorny and the going is expensive and slow.

part during absorption from the gut, presumably by bacteria [74]. Dehydrogenation has not been demonstrated. (3) The long-chain fatty acids are tightly bound to albumin, but no significant differences in binding of long-chain saturated

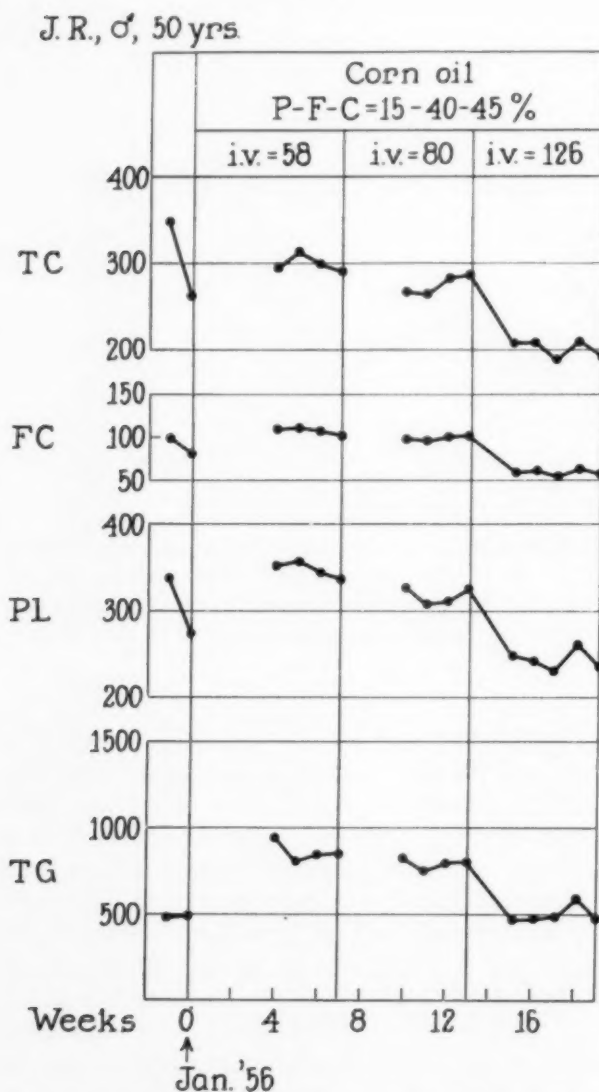


FIG. 6. Effect of ingestion of corn oil hydrogenated to iodine values of 58 and 80, compared to unhydrogenated oil. Levels of TC and PL significantly different ($p < 0.01$) in all three test periods. Fifty year old man with history of myocardial infarction.

Mechanisms. Fatty acids: What evidence exists to suggest that different fatty acids are metabolized through different pathways? (1) Saturated and unsaturated fatty acids in a mixed fat meal are equally well absorbed [74]. The acids of chain length C_{2-12} are absorbed mainly via the portal vein, however, while C_{14-18} acids are absorbed entirely via the lymphatic system [17]. (2) Unsaturated acids are hydrogenated in

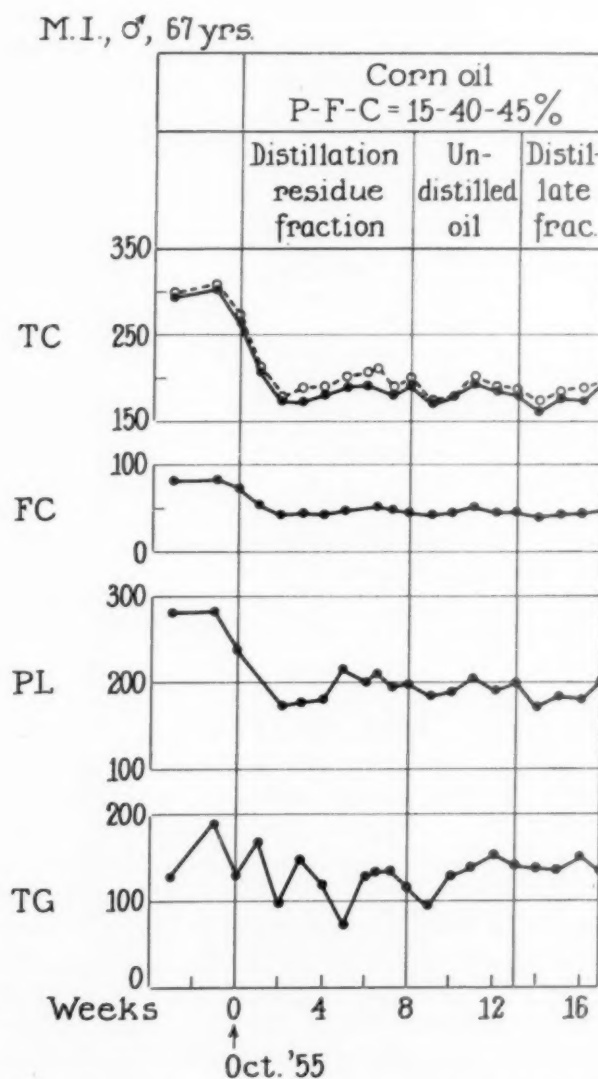


FIG. 7. Lack of dietary effect on serum lipids of sixfold difference in non-saponifiables of corn oil. Molecular distillation enriches non-saponifiables in distillate fraction; residue fraction is poor in this material. Sixty-seven year old man with history of coronary insufficiency.

and unsaturated acids have been found [75]. (4) The essential fatty acids are those with at least two double bonds, 6 and 9 carbon atoms from the terminal (or methyl) end of the chain. Utilizing his "6-9 terminal" hypothesis, Thomasson [73] has identified a number of essential acids in addition to linoleic and arachidonic acids. Klenk [76] has demonstrated that the highly unsaturated acids of fish and animal

sources have the same chemical structure. (5) The turnover of unsaturated acids is said to be slower than that of saturated acids in rat liver and rat carcass [77]. (6) In natural lecithin the unsaturated acids are preferentially esterified at the alpha carbon of glycerol [78], while in most triglycerides these acids are found in the beta position [79]. In Kennedy's classic work on the enzymatic synthesis of triglycerides and phospholipids, the common diglyceride precursors must contain at least one unsaturated fatty acid [80]. This may be only an *apparent* enzyme requirement, for the insolubility of the fully saturated diglyceride substrate may hinder the approach of the enzyme to it. If the enzyme requirement is specific, there may be a metabolic distinction between saturated and unsaturated acids, residing in their physicochemical properties. (7) The enzymatic esterification of cholesterol in the human intestinal lumen is more rapid with unsaturated fatty acids than with saturated acids [81]. (8) The metabolic role of the essential fatty acids is still unknown. Two laboratories [82,83] found uncoupled oxidative phosphorylation in essential fatty acid deficiency. Deuel [84] has enumerated a large number of physiologic actions of these acids. Holman [85] believes they serve an important transport function for serum cholesterol.

These considerations strongly indicate that the metabolism of saturated and unsaturated acids may be different, and that the accessibility of these acids to enzymes may determine some part of this difference. Any general physicochemical difference, such as solubility or molecular shape, might determine *some* features of their different metabolic behavior, but the astonishing specificity of the 6-9 terminal structure of essential fatty acids puts these acids in a special category.

Lipsky et al. [86] in 1955 demonstrated in man that the turnover of non-phospholipid fatty acids, (i.e. cholesterol ester or triglyceride fatty acids, or both) is more rapid than that of the phospholipid acids. In 1957 James et al. [87] identified the fatty acids in the same two ester groups (phospholipids and non-phospholipids) in normal subjects and in patients with coronary heart disease by gas-liquid chromatography, without finding significant differences.

Preliminary studies [63] of the individual fatty acids of triglycerides, cholesterol esters and phospholipids have been made in our laboratory. We considered it essential to have rigid control

of the dietary intakes of patients whose serum lipids were so fractionated and made the measurements only after the patients had reached a "steady state" on a given dietary mixture [62]. It was clear that (1) the fatty acid distributions of all ester groups were markedly affected by

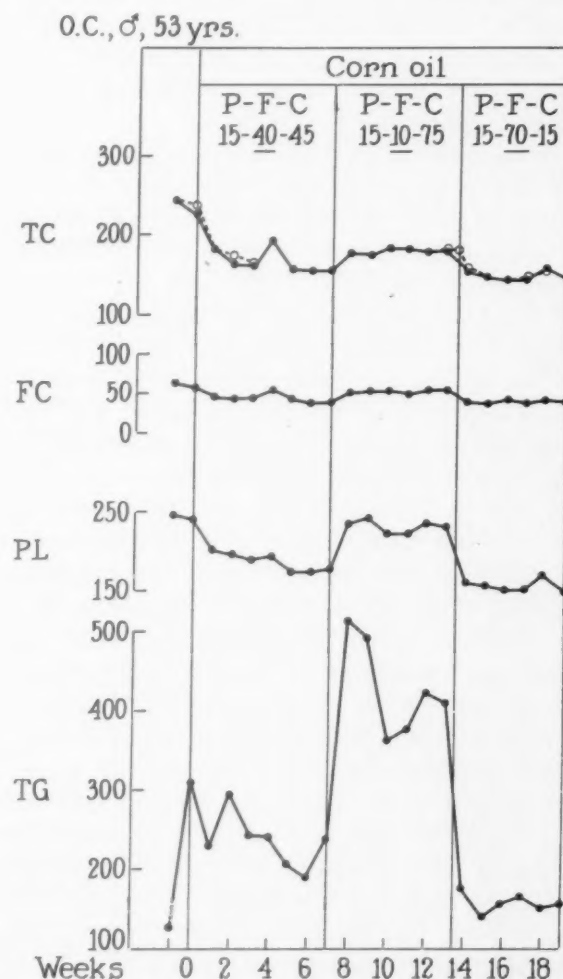


FIG. 8. Effect on serum lipids of varying the proportions of fat and carbohydrate calories reciprocally, keeping total calories, protein and body weight constant. Major changes were produced in serum triglycerides, smaller effects on phospholipids, least striking differences in cholesterol. The lowest serum lipid levels occurred on highest intake of corn oil. Fifty-three-year old man with history of coronary insufficiency.

changes in dietary fat, (2) the triglyceride fatty acids were most responsive to dietary manipulations and most closely resembled in fatty acid composition that of the fed fats, (3) the major part of the serum arachidonic acid was found in the phospholipid fraction, and (4) the cholesterol ester fatty acids were the most unsaturated of the three groups when butter was the sole dietary fat, but the triglyceride fatty acids were

the most unsaturated when corn oil was fed. A more complete description of the changes in these acid groups produced by diet will form the basis for subsequent turnover studies.

Cholesterol: It may reasonably be asked what becomes of the cholesterol and phospholipids which decrease in concentration in the serum when certain dietary fats are fed. Are they metabolized more rapidly? excreted more rapidly? synthesized more slowly? sequestered in some tissue other than serum?

An exploration of synthesis rates of cholesterol was made in 1956 with Drs. Hellman and Rosenfeld in an experiment in which the incorporation of 2-C¹⁴-acetate into free and esterified cholesterol was measured. The time-curves were measured during two dietary periods when the serum cholesterol was held at two different levels. The data obtained were not significantly different in the two periods: per cent incorporation into free or ester cholesterol, time of peak incorporation, time of crossover of free and ester cholesterol curves, or slopes of the decay curves. These results do not support the contention that the two dietary fats may have different effects on cholesterol synthesis. However, Hellman et al. [88] previously noted large individual variations in acetate incorporation into cholesterol, in view of which it would be necessary to obtain at least fourfold differences before significance could be claimed.

A second experiment was carried out with Drs. Hellman and Rosenfeld to measure the excretion of cholesterol in different dietary periods. A patient whose serum cholesterol level was 900 mg. per 100 ml. serum on an *ad libitum* diet was given radioactive cholesterol (4-C¹⁴-cholesterol) intravenously in order to label the body pools of readily exchangeable cholesterol. A "balance study of labelled sterols" was carried out, to tell whether or not the excretion of the body's readily exchangeable cholesterol into the feces was altered by the feeding of different dietary fats. The findings, reported in preliminary form [89], indicated that when serum cholesterol concentrations rose (on butter feedings) the fecal sterols decreased by almost the same amount; when serum cholesterol fell (on corn oil feedings) the fecal sterols increased by almost the same amount. Thus the net gains and losses in serum cholesterol could be accounted for almost completely by the changes in fecal excretion of the labelled sterols. These results indicate that excretory mechanisms may

explain the changes in serum levels of cholesterol which are produced by exchanges of dietary fats. It remains to be determined whether this is due to increased excretion of cholesterol into the gut, or to decreased reabsorption of cholesterol from the gut. The data fail to substantiate the possibility that cholesterol is sequestered in some other tissue (? arterial intima) when its concentration in the serum decreases in response to a change in dietary fat. The ratio of labelled bile acids/labelled sterols decreased when corn oil feedings caused the serum cholesterol to fall. Thus we have no indication that this conversion was accelerated when corn oil was the sole dietary fat. The results of the two isotope experiments are in agreement in diverting our attention from synthesis rates to excretory mechanisms.

Bile acids: Other laboratories have attempted to gain an understanding of the mechanisms underlying alterations in serum cholesterol levels by measuring the output of bile acids in the feces under various dietary conditions. Although serious methodologic difficulties handicap such efforts, the Capetown group [64] has presented preliminary data which suggest that the excretion of fecal bile acids increases when exchanges of dietary fats cause serum cholesterol levels to decrease. Their results are compatible with those of the labelled sterol balance study already described.

Dietary Cholesterol. Keys et al. [90] in 1956 summarized a wide experience which led them to the conclusion that dietary cholesterol has no important effect on serum cholesterol levels. This conclusion was based on (1) long term observations of men eating diets low and high in cholesterol, (2) epidemiologic survey data in Minnesota and Sardinia where dietary intakes of cholesterol vary widely, (3) experiments in which men doubled or halved their cholesterol intakes for many months, (4) experiments in which 500 or 600 mg. per day of cholesterol was added to a rice-fruit diet, and (5) experiments which tested threefold variations in cholesterol intake in mixed food diets containing 66 gm. of total fat per day. They concluded that the independence of serum cholesterol levels and cholesterol intakes demonstrated by them in adult men over the whole range of natural human diets probably also applied to infants, children and women.

Other workers have purposely added considerable amounts of cholesterol to diets containing vegetable fats in an effort to demonstrate

whether or not the depressions in serum cholesterol and phospholipid levels caused by these diets might be due to an *absence* of dietary cholesterol. Thus Kinsell in 1952 [47] stated that the addition of 30, then 60 gm. per day of crystalline cholesterol to a tube-fed formula diet consisting of 62 gm. of protein and 195 gm. of vegetable fat caused no elevation of serum cholesterol. His experiment was twelve days in duration. Bronte-Stewart et al. [64] added 3 gm. of cholesterol per day to their food mixtures without losing the cholesterol-depressant action of unsaturated fats. Ahrens et al. [62] showed that when serum cholesterol levels were depressed by feeding 40 per cent of calories as corn oil, the addition of 2 gm. per day of cholesterol produced no significant elevation in serum cholesterol levels; however, the administration of 4 and 8 gm. per day led to small but significant increases in cholesterol and phospholipid levels. Test doses of cholesterol (600 mg. per day) in the range of normal human intakes added to formulas containing 40 per cent of calories as lard also failed to evoke a further elevation in serum cholesterol concentration. These various studies confirm Keys' conclusions and in addition demonstrate that the effectiveness of unsaturated type dietary fats in depressing serum lipid levels is not due solely to absence of cholesterol from those diets.

In view of the low percentage absorption of cholesterol in human beings [91] it is entirely possible that a considerable amount of cholesterol could be absorbed without causing a significant change in serum levels [92,93]. The possible tissue deposition of cholesterol which is slowly absorbed certainly cannot be excluded on the basis of serum studies. A simple test of this possibility is not available. It is not feasible to carry out accurate cholesterol balance studies by comparing dietary intake and fecal output in the usual manner [94]. An unknown amount of cholesterol is synthesized each day by the liver; cholesterol is converted in the gut into other products which are difficult to measure; and in the body, cholesterol is eventually converted to bile acids, the excretion products of which are exceedingly complex [95]. Stanley and Cheng [96] have devised an ingenious method for calculating the intestinal secretion, absorption and excretion of cholesterol which may clarify some of the questions in this area. The chemical methods recently developed for measurement of fecal sterols by Coleman et al. [97] also may prove helpful. Central to this issue is further

study of the quantitative aspects of bile acid metabolism which Lindstedt and others in Bergström's group [98] have recently elucidated most productively. The technic of a labelled sterol balance study described by Hellman et al. [89] also may be expected to add valuable information in an area which is still largely undefined.

Thus, while it can be stated with considerable assurance that serum cholesterol levels *ordinarily* are independent of dietary cholesterol intake in man, much remains to be learned about the metabolism of ingested cholesterol.

Other Dietary Sterols. Sperry and Bergmann [99] in 1937 showed in mice that the oral administration of sitosterol produced a lowered content of cholesterol in the liver. In 1951 Peterson [100] reported that in chicks the addition of mixed soybean sterols to a cholesterol-rich diet prevented the expected hypercholesteremia. Numerous later studies confirmed these findings in other laboratory animals, and evidence was given that cholesterol-induced atheromatosis could be prevented. It was shown [101-103] that the effect of vegetable sterols in animals was mediated through interference with cholesterol absorption, perhaps due to interference in the esterification of cholesterol prior to its absorption.

Clinical studies performed by Best et al. [104] established that in man the administration of beta-sitosterol caused significant decreases in serum cholesterol levels. The higher the initial level of cholesterol, the greater the decrease during sitosterol administration. Their results were confirmed by Farquhar et al. [105] and Sachs and Weston [106], but Wilkinson et al. [107] found no effect and numerous other authors have had irregular results. No study other than Wilkinson's has been carried out under metabolic ward conditions, and it remains uncertain whether total food intake and the composition of the food mixture itself are altered by the ingestion of emulsions containing this plant sterol. It has not been explained why it is necessary to administer such large amounts of this sterol (at least 18 gm. per day) to obtain the effects described, since this is at least six times the amount of cholesterol which passes into the gut each day in the diet and via the bile [108]. In animals, 2:1 ratios of beta-sitosterol/cholesterol sufficed to inhibit cholesterol absorption [109], even though cholesterol was fed in large amounts.

Beveridge et al. [71] reported that as little as

2 gm. of beta-sitosterol administered to normal young men on a fat-free diet for eight days caused large decreases in serum cholesterol levels. Since this decrease was as great as that produced by feeding 60 per cent of calories as corn oil (which was stated to contain an equivalent amount of sitosterol, or 2 gm.), they reasoned that the depressant action of corn oil ingestion on serum cholesterol levels was due to its sitosterol content. However, on a low fat diet the enterohepatic circulation of cholesterol is considerably diminished [110], and it may be that on Beveridge's fat-free diet the 2 gm. of sitosterol administered was sufficient to interfere with a greatly reduced secretion of cholesterol into the gut. The effect of the 2 gm. in the 60 per cent corn oil diet may have been quite dissimilar.

A number of other sterols have been fed to animals with the intention of interfering with cholesterol absorption. The rationale is based in part on the original observations by Schönheimer [111] that plant sterols are completely non-absorbable. However, it is now found that dihydrocholesterol is absorbed by rabbits, as is Δ^7 -cholesterol (lathosterol) and 7-dehydrocholesterol, and all may produce atheromas [112]. Dihydrocholesterol also may cause biliary concretions and inflammatory lesions of the biliary tract in rabbits [113]. Beta-sitosterol was found to be absorbed by rats and by man; in the rat, unlike dihydrocholesterol, it was not stored [114].

In an effort to decrease cholesterol synthesis in liver, Steinberg and Frederickson [115] fed Δ^4 -cholestenone for long periods to rats. Toxic effects were noted, with marked adrenal hypertrophy and storage of sterol (presumably, its end product, dihydrocholesterol) in the liver. However, it is interesting that cholesterol synthesis was depressed.

It seems fair to state that an effective non-toxic cholesterol "analogue" has not yet been found, either for the suppression of cholesterol synthesis or of cholesterol absorption in the gut. Interesting studies on sterol derivatives which might serve as competitive inhibitors in the growth of German cockroaches have been described by Noland [116]. He noted that thiocholesterol was extremely active in this regard.

Intravenous Fat Emulsions. Parenteral alimentation by means of intravenous fat infusions, reviewed recently by Meng [117], causes considerable elevations in serum triglycerides during

and after the infusion. The administered fat is cleared rapidly, and the serum triglyceride levels of normal men return to pre-infusion levels in twenty-four hours. Serum cholesterol levels in normal men are not significantly altered. Geyer et al. [118] showed in dogs that the fat in these emulsions was rapidly metabolized to carbon dioxide.

Lever and Waddell in 1955 [119] observed that the responses to intravenously administered fat emulsions were different in normal men, in hypercholesteremic patients and in hyperlipemic patients. Single infusions of a 500 ml. emulsion containing 50 gm. of oil (cottonseed oil or synthetic triolein), 25 gm. dextrose, 6 gm. soybean phosphatide and 1.5 gm. of a synthetic surfactant, pluronic, were tested. Clearing of the expected triglyceride elevations in the fourteen normal subjects and four hypercholesteremic patients was noted twenty-four hours after the infusion, whereas seven of nine hyperlipemic patients had higher triglyceride levels than before the infusion. Cholesterol levels were not affected in the normal subjects whose initial concentrations were below 300 mg., while those four of fourteen with pre-infusion levels above 300 mg. showed a mean decrease of 70 mg. The cholesterol levels in the hyperlipemic subjects showed decreases averaging 97 gm., with most marked effects in those whose cholesterol levels exceeded 400 gm. before infusion. The four hypercholesteremic subjects had cholesterol levels ranging from 515 to 590 mg. before infusion; twenty-four hours after infusion these levels decreased on the average 120 mg.

Daily infusions were given for one week to two hypercholesteremic patients and three hyperlipemic patients. Cholesterol, phospholipid and triglyceride levels gradually decreased under this management in all patients, and the decreases were uniformly striking. The effects were temporary, and within three weeks levels in all patients had markedly increased.

Lever and Waddell [119], after testing emulsions made up without oil, concluded that the non-fat ingredients were not responsible for the effects observed. Subsequently, however, Waddell [120] has found that infusions of 5 per cent dextrose cause fairly regular decreases in all lipid classes in hyperlipemic subjects, hypercholesteremic subjects and in normal men. He is currently evaluating this interesting interrelationship of carbohydrate and fat metabolism.

His observation recalls the striking effects of carbohydrates on serum levels of non-esterified fatty acids noted by Dole [127] and by Gordon [122]. Waddell also has found decreases in serum lipid levels in some patients with infusions of pluronic in dextrose, or phosphatides-pluronic-dextrose.

There has been no published evidence of sequestration of serum lipids in other tissues, following fat infusions. It is believed on the basis of dog experiments [118] that the infused fat and that which disappears from the blood stream are both rapidly metabolized.

Subsequent to the original report, Herbst, Lever and Waddell [123] showed significant increases in the electrophoretic mobilities of the serum lipoproteins following fat infusions. Since the same effects had been noted after heparin injections, they postulated that the infusion of fat also may trigger a release of clearing factor.

This new approach may aid in understanding the abnormalities which lead to hyperlipemia and hypercholesteremia, but it is not proposed as a practical therapeutic measure.

Hydrogenated Fats. The postulated increase in incidence of ischemic heart disease since World War I is linked by some [124] to the increased use of margarines prepared by partial hydrogenation of vegetable fats. Following the suggestion in 1955 [40,41] that serum cholesterol levels in man might be related to the degree of unsaturation of the dietary fat, it became tempting to think that the destruction of essential fatty acids by hydrogenation, and the formation of so-called "unnatural" isomers, might lead to harmful effects upon ingestion. This reasoning is based on three unquestioned facts: the finding [125] that *cis-trans* and *trans-trans* isomers of linoleic acid cannot replace *cis-cis* linoleic acid in remedying essential fatty acid deficiency; the presence of heavy concentrations of *trans* acids in hydrogenated products [126]; and the large consumption of margarines throughout the Western world.

Mann [6] has shown that there is serious question whether or not the incidence of ischemic heart disease has actually increased. Yudkin points out [4] that the incidence of ischemic heart disease in various populations does *not* parallel the use of margarines. Thus, Norway, in which the per capita consumption of margarine is three times that of the United States, has less than one-third our incidence of this disease.

The ingestion of hydrogenated fats produces

somewhat higher serum cholesterol and phospholipid levels in man than the unhydrogenated oil; this has been shown by Bronte-Stewart [64], Ahrens [62] and Malmros [68]. However, these experiments demonstrate only that the effects observed are correlated with the over-all loss of many of the double bonds of the natural fat. The effect of specific isomers of linoleic and oleic acids on human serum lipid levels has never been critically tested. Therefore, there is no direct evidence that the isomers have a different effect on these levels than the parent acids.

The term "unnatural isomer" deserves comment. Shorland and Hansen [127] have shown in numerous studies that all ruminant depot fats contain significant amounts of branched-chain fatty acids as well as odd-numbered acids (perhaps 5 per cent of the total acids). It is believed that bacterial action in the rumen is responsible for the production of these acids. They are then deposited in the animal's depots, and are natural components of the fat of mutton, goat and beef. Their small concentration in these fats suggests that they are metabolized. Current studies of human fatty acid mixtures [128] have demonstrated the normal occurrence of branched-chain and odd-numbered acids, as well as numerous positional isomers of oleic acid [129]. It would be profitable to study the metabolism of these components.

The use of hydrogenated fats as the sole source of dietary fat in the rearing of forty-six successive generations of rats was shown by Alfin-Slater et al. [130] to have produced no demonstrable ill effect on growth, longevity, reproduction, lactation, litter size and other parameters. It may not be justified to extend these findings to man unreservedly, since the rat is relatively resistant to the experimental production of atherosclerosis.

Heated and Oxidized Oils. Under conditions of economic stress after World War II highly unsaturated fish oils, thermally treated to get rid of undesirable tastes, were included in commercial food products, although it was well known that thermal treatment of oils produces polymerization. When it became apparent that "heat-bodied" oils were not acceptable for human consumption, this practice (largely confined to the Scandinavian countries) was rapidly discontinued. Nevertheless, there continues to be an interest in the possible formation of toxic products during the heating of edible oils, as during deep fat frying. Kummerow has

partially polymerized a number of edible oils and has isolated products which were toxic for rats. He and his colleagues have recently proposed [131] that these products exert their toxicity by destruction of pyridoxine and riboflavin, since supplementation with these substances partially counteracted the toxicity of the polymerized fats. They claimed that, although heat polymerization and oxidative polymerization result in different toxic products, both insults may occur in the course of commercial food frying. Melnick [132], in defense of commercial frying practices, noted no change in iodine value of frying oils sampled in a large number of potato chip factories, and considered this to be adequate proof that polymerization did not take place under practical conditions. The experimental studies of Crampton et al. [133], Kaunitz and Slanetz [134], and Kaneda et al. [135] are pertinent.

The practical importance of heat damage to unsaturated oils remains to be established. Nevertheless, the chemical changes in fats which *might* be produced by various cooking conditions have not been defined. As unsaturated fats are incorporated more widely in everyday diets, it becomes increasingly imperative that such studies be carried out.

Acute Effects after High-Fat Meals. Clotting: Duncan and Waldron [136] in 1949 were among the first to demonstrate that after ingestion of a fat meal the coagulation time of whole blood is significantly shortened. They suggested that this phenomenon might explain the high incidence of coronary heart disease in hyperlipemic states like diabetes. In 1953 Fullerton et al. [137] confirmed this finding with two tests: the clotting of whole blood in silicone tubes, and an accelerated one-stage prothrombin time (Stypven time, using Russell's viper venom as thromboplastin). They discussed at length the concept that hypercoagulability of the blood following fat meals might play an important role in the pathogenesis of thrombosis and complications of atherosclerosis. A vast amount of research has been stimulated by their provocative paper.

In 1955 Poole [138] concluded that chylomicrons hastened the clotting of recalcified citrated plasma. In later studies [139,140] Poole and Robinson demonstrated that the factor in chylomicrons which caused this phenomenon, as well as increased Stypven times, was its phosphatide. They identified the active component as phosphatidyl ethanolamine, and stated

that lecithin, phosphatidyl serine and inositol phosphatide were inactive. O'Brien [141] in 1955 concluded that chylomicrons activated the Stypven test, but neither he nor, later, Buzina and Keys [142] were able to relate the clotting time changes to the curve of lipemia. In 1956 O'Brien [143] confirmed the finding that phosphatidyl ethanolamine in exceedingly small concentrations activated clotting *in vitro*. He found in human volunteers that ingestion of 50 gm. of butter, margarine or a "vegetable cooking fat" all produced equal acceleration of the Stypven time, but that one-third as much egg yolk fat caused an even greater acceleration. In 1957 he [144] reported that four fats of widely varying degrees of unsaturation caused equal reductions in clotting times, and that test meals containing equivalent amounts of phospholipids (soybean phospholipids or egg lecithin) had a still greater effect. He postulated that a part of the phospholipids, absorbed intact without hydrolysis [145], might cause these effects. He obtained no clear relationship between total phospholipid levels in the serum and clotting times, but this negative result would be expected if only one of the several serum phosphatides is primarily reactive. MacLagan and Billimoria [146] studied the addition of various foods to the Stypven test system and concluded that milk products had a unique accelerating effect.

The potential importance of these findings demands that further exploration be made of (1) the striking hypercoagulability of blood after meals containing eggs, (2) the site of action of specific phosphatides in the complex chain of events which is termed "clotting," and (3) the relationship between clotting activity as measured outside the body and the phenomenon of thrombosis itself. O'Brien [147] found no demonstrable difference in Stypven times after fat meals in twenty male patients with coronary thrombosis and twenty age-matched male volunteers, and noted that "blood coagulation studied in the test tube may have little relevance to the *in vivo* formation of a thrombus." However, McDonald and Edgill [148], studying forty-eight patients in each group, found statistical differences in a number of clotting indices. They could not state with certainty whether the increased coagulability in the coronary patients was cause or effect of their disease. When values of individual patients were compared, there were broad overlaps; thus, it was not possible to predict thrombotic tendencies in any given patient.

It is clear that further progress is hampered by technical difficulties in the testing methods, and it is hoped that more direct and meaningful assays may be developed as the mechanisms of clotting are better understood. It may then be possible to obtain a clearer picture of the time-course curve of change in clotting activity after fat meals, and perhaps to relate it to some aspect of phospholipid metabolism.

Fibrinolysis: Greig [149] reported in 1956 that the ingestion of a high fat meal (butter, eggs, bacon) by healthy volunteers caused a significant reduction in fibrin clot lysis *in vitro*. The degree of inhibition of *in vitro* fibrinolysis after a fat meal was decreased by exercise and was reversed after intravenous injection of heparin. When corn or peanut oils constituted the test fat meal, there was no inhibition of fibrinolysis.

In a recently reported extension of these findings, Greig and Runde [150] found that the ingestion of all vegetable oils, regardless of degree of unsaturation, activated fibrinolysis, while egg yolks and butter fat inhibited it. When lipids were removed from the serum by various solvents and the residues tested for fibrinolytic activity, the fibrinolytic system was reactivated. The degree of reactivation was most striking in the serums of patients fed egg yolk and butter fat, least effective in the case of all vegetable fat feedings.

Greig postulates that feedings of butter and of egg yolk lead to the presence of a type of serum lipoprotein which inhibits fibrinolysis. It is tempting to speculate that *in vivo* fibrinolysis may also be affected by the feeding of different types of fat. In studies of hypercoagulability, cream [146] and egg yolk [144] seemed to show striking differences from the other oils. In both systems (fibrinolysis and coagulation) differences could not be related to the degree of unsaturation of the dietary fat. Qualitative differences in serum lipids seem more determinant in both systems than quantitative differences.

Blood viscosity: Changes in viscosity of the blood following fat meals have been noted by Swank, as well as increased adhesiveness and aggregation and decreased sedimentation rates of red blood cells [151-154]. He also studied the sludging of blood and changes in the capillary bed in the hamster cheek pouch by means of motion picture records of these responses to fat meals. Aggregation of chylomicrons was noted six to nine hours after a heavy fat meal in volunteers; this was

much less marked when unsaturated fats were fed in the test meal than in the tests with saturated fats [151]. It is interesting that all these phenomena occurred several hours after the peak of lipemia [153].

The failure of Watson [155] to find any alterations in blood viscosity of patients after ingestion of cream must be reconciled with Swank's findings. It is possible that the lack of sensitivity of Watson's viscosity method masked the effects he was studying.

Angina pectoris: Kuo and Joyner [156] in 1955 reported a detailed study of the response of fourteen patients with coronary insufficiency to a test meal of butter fat (0.6 gm. per pound body weight). In six patients angina pectoris developed postprandially, with pain at the peak of lipemia. Electrocardiographic changes were demonstrated in four. The administration of a non-fatty meal to three of the reactive patients failed to produce angina. The authors concluded that patients with coronary insufficiency may benefit from a low fat diet, since in such patients postprandial lipemia may have a deleterious effect on the myocardium.

In our experience over the last five years, at least thirty patients have been maintained at constant body weight for periods of four to forty months by means of orally administered liquid formulas which contained various proportions and types of fat [62]. Their daily intakes were usually divided into five feedings. They received a maximum of 70 per cent of calories in the form of fat (or about 0.25 gm. fat per pound body weight five times per day), which might be either corn oil or butter oil or other fats. The most commonly used formulas contained 40 per cent of calories as fat (or about 0.14 gm. fat per pound five times per day). We have never seen any pattern of postprandial angina which could be correlated with the peak of lipemia. In fact, as noted and qualified previously [62], our patients have usually displayed much less angina during their management in the hospital on these formula diets. However, the much larger fat load administered by Kuo and Joyner may explain the results they described, since in a single meal they administered 90 gm. of fat to a 150 pound patient. This dose comprised 810 calories, or 34 per cent of the day's calories, taken in one meal. Their experience would suggest that it may be unwise for patients with coronary insufficiency to gorge on fat. The phenomena described are indeed interesting,

and it is hoped that further studies will explain whether or not the changes in viscosity of blood described by Swank [153] may explain this syndrome. It would be valuable to know whether or not all types of fats cause comparable effects.

For reasons to be discussed (see section on Carbohydrate), we believe that low fat diets may be undesirable in some patients.

PROTEIN

Our understanding of the effects of dietary protein on serum lipid levels is fragmentary. A considerable part of our confusion has been created by the use of numerous species of animals in countless variations of experimental design. It is compounded by lack of complete understanding of protein requirements of growing and adult organisms, and by the complexities created by the need to achieve a proper balance of amino acids in the diet [18,157]. Nevertheless, it is clearly important to clarify the relationship of dietary protein to serum lipid levels: Yudkin [4], Yerushalmy and Hilleboe [5] and Olson et al. [158] have pointed out the correlation which can be drawn between animal protein intake and the incidence of ischemic heart disease. It is essential to determine when this correlation is primary, that is, with dietary protein itself, and when secondary, namely, with the type of fat which is an integral part of animal protein foods.

Dietary protein apparently affects serum lipid levels in at least two ways. If there is a deficiency of labile methyl groups in the diet of rats, *hypo*-cholesteremia develops as the liver accumulates fat, even when the diet also contains cholesterol [159,160]. This hypocholesteremia is not affected by type or quantity of dietary fat [158]. Thus, it appears that hypercholesteremia cannot develop with cholesterol feeding unless the diet contains an adequate supply of labile methyl groups. Possibly, the synthesis of phospholipids is limited, since choline is an integral part of lecithin and sphingomyelin. There may be human counterparts of this deficiency state. In areas where dietary protein is inadequate in quantity or quality, or when the rice diet is administered, serum cholesterol levels often are exceedingly low.

Secondly, it appears that the feeding of protein deficient in sulfur (i.e., alpha-protein of soybeans) leads to *hyper*cholesteremia in cholesterol-fed monkeys [161]; here, again, choline also is limiting. The studies of Portman and

Mann [162] showed that this type of sulfur deficiency inhibits the production of taurine, and thence of taurine-conjugated bile acids. When the conversion of cholesterol to taurine-conjugated bile acids is limited by sulfur deficiency in the diet, cholesterol accumulates in the plasma. It seems likely that the so-called "protective" effect of dietary protein against hypercholesteremia in cholesterol-fed chicks, reported by Kummerow et al. [163] and Moyer et al. [164], is due to increased sulfur requirements for conversion of cholesterol to bile acids. This mode of action may also explain the hypercholesteremia in cholesterol-fed rats on low protein, high choline diets, which Jones et al. [165] described.

On the other hand, the hypercholesteremia produced in old rats on high casein diets by Jones and Huffman [166] has not been explained. It may be due to a relative deficiency of some nutrient caused by the excess intake of this unbalanced protein. These experiments deserve confirmation and extension; coronary atheromas developed in one-third of their rats.

Keys and Anderson [19] in 1957 reported experiments dealing with dietary protein and serum cholesterol levels in man. Two experiments were carried out on physically healthy schizophrenic men under metabolic ward conditions for sixteen or more weeks. In the first, two levels of dietary fat (16 and 39 per cent of total calories) were tested at two levels of dietary protein (11 and 20 per cent of total calories). No significant differences in serum cholesterol levels were produced by the two protein intakes at either fat level. In the second experiment, protein intakes of 8 and 18 per cent were compared (with 19 per cent of calories as fat in all periods). Again no significant differences in serum cholesterol levels were detected. These experiments give a clear *negative* answer to one question: does increasing the intake of protein from a level generally recognized as adequate for maintenance of health in adult man to a still higher level cause any change in serum cholesterol levels? However, it seems unwarranted to extend these findings to diets containing lower protein intakes than they actually tested, especially to ones which may be sub-optimal. The statement that "the results of the present study do not afford confirmation to the suggestion that the low cholesterol values in populations living on low fat intakes are in any way related to the amount or kind of protein in

their diets" may be misleading. Olson et al. [158] commented on the possibility that the rice diet (25 to 30 gm. protein per day), with its well recognized hypocholesteremia, may be sub-optimal in protein. In a well controlled experiment in seven men, they were able to produce hypocholesteremia with a low protein, moderate fat diet [167]. Hatch et al. [168] demonstrated abnormalities in bromsulfalein retention and in free-to-total cholesterol ratios in patients on the rice diet.

In short, it is not clear that the low cholesterol levels seen in populations eating diets very low in fat may not be due in part to low intakes of protein.

CARBOHYDRATE

A number of experiments have been carried out in this laboratory [62] which explored the effects of variations in dietary carbohydrate at the expense of dietary fat. Figure 8 demonstrates that when corn oil made up only 10 per cent of total calories, there was a sudden marked increase in serum triglyceride levels as well as a small rise in phospholipid and cholesterol levels. When the corn oil intake was increased to 70 per cent of total calories, there was a prompt fall in triglyceride and other lipid levels. Thus the lowest serum lipid levels occurred on the highest intake of corn oil.

Similar changes have been produced in four other patients. In the oldest of these, a seventy-two year old woman with coronary insufficiency, there was a fourfold increase in the serum triglyceride level when a formula containing 70 per cent of calories from corn oil was replaced by a diet free of fat [63]. In addition, there was marked lipemia on the fat-free diet and a striking increase in $Sf_{>20}$ lipoproteins. It remains to be determined whether or not this response is a function of age; less dramatic effects on triglycerides were produced by these dietary alterations in a thirty-three year old hypercholesteremic man. Hatch and associates [168] also noted a rise in the triglyceride level and abnormal ultracentrifugal patterns in patients fed rice diets low in fat. The brief note of Nichols et al. [169] confirms our findings in part; they noted major elevations in Sf_{20-400} lipoproteins when a high carbohydrate, low fat diet was eaten. Such experiments demonstrate that the various serum lipid levels need not vary in a parallel manner and that a total cholesterol value may give little indication of the other

lipid levels. Since in some patients a diet low in fat produces high levels of serum triglycerides, we are tempted to ask whether or not the lower density lipoproteins are less "atherogenic" than the higher density lipoproteins rich in cholesterol and phospholipids. We know of no solid evidence on this point, and until this is further explored we question the wisdom of prescribing very low fat diets for the general population.

Yudkin's [4] analysis of factors related to the incidence of ischemic heart disease showed a better relationship with intake of sugar than with any other major foodstuff. The intake of simple sugars and conversely of complex polysaccharides (starch) unquestionably varies from region to region. Those peoples who subsist largely on tubers, cassavas and other starchy foods probably eat less sugar *per se* than the wealthier, more civilized peoples. Yet, in the latter group, while total carbohydrate intake is much lower, a large proportion of this intake undoubtedly consists of simple sugars. Thus the people who are said to have the lowest incidence of ischemic heart disease eat diets characterized by (1) lowest total protein and animal protein intakes (which might cause low serum cholesterol levels because of suboptimal intakes of labile methyl groups), (2) lowest total fat intakes, and probably a higher ratio of unsaturated to saturated fats (both factors might serve to depress cholesterol and phospholipid levels), and (3) highest intakes of carbohydrates, of which the largest part is starchy.

In the light of these considerations, an observation made by Foster, Hooper and Whipple [170] in 1919 assumes some importance. They noted that in dogs the excretion of bile acids was markedly reduced by feeding diets containing simple sugars. Portman, in his analysis of the factors influencing bile acid excretion in rats, has greatly extended the original findings of the Whipple group. In 1955 he showed [171] that when dextrose or sucrose was substituted in the diet isocalorically for corn starch, the total bile acid excretion decreased. The output of cholesterol and of total bile acids in the bile of rats fed a purified diet containing sucrose as the sole carbohydrate was smaller than when Purina Chow was fed. These findings suggested that the feeding of simple sugars affected the conversion of cholesterol to bile acids in some manner, and that the degree of experimental hypercholesteremia might be influenced by the type of

carbohydrate feeding. Later experiments [172] demonstrated that when corn starch replaced sucrose, glucose or fructose isocalorically, the serum cholesterol levels of cholesterol- and cholic acid-fed rats were considerably lower. The addition of sulfasuxidine to the diet to reduce the bacterial flora in the gut abolished the hypocholesteremic effect of starch. Findings contrary to or confirming Portman's data in rats have not appeared, but Grant and Fahrenbach [173] in studies of cholesterol-induced hypercholesteremia in chicks have found that the response to glucose and sucrose were strikingly different; cholesterol levels were higher on the sucrose diets.

Since Portman's data indicate that the intestinal bacteria may play an important role in the phenomenon described by him, one might expect considerable species differences to appear as these studies are extended. In our investigations of serum lipid levels in man, we have noted no significant differences caused by isocaloric exchanges of sucrose, dextrose and dextrans, but we have not carried out tests with starches. In this connection it should be mentioned that the digestibility of starches of various sources may be very different [174].

INTESTINAL BACTERIA AND "BULK"

It is appropriate that this review should include a brief consideration of the factors which influence intestinal bacteria, and the possible role that these bacteria may play in affecting serum lipid levels. In the previous section it was noted that the different effects of corn starch and simple sugars on serum cholesterol levels of rats were abolished by administration of sulfasuxidine [172]. Cholesterol is degraded eventually to bile acids [175] and in the gut the bile acids are chemically altered by the bacteria with the production of materials which probably are not reabsorbed. Thus the method for disposal of cholesterol is highly complex and depends finally on the action of the intestinal flora. In germ-free rats this mechanism is non-existent, and the half-life of the bile acids is greatly prolonged [176]. Reabsorption of undegraded bile acids unquestionably affects the rate at which cholesterol is converted to bile acids in the liver.

In addition to these events, bacteria are also responsible for the conversion of cholesterol to coprosterol in the gut [177-179]. While the former is slowly reabsorbed, the latter is considered to be completely non-absorbable. If

cerebrosides are administered in the diets of rats, this conversion of cholesterol to coprosterol is accelerated. If sulfasuxidine is given, this conversion is inhibited. Modern concepts of the conversion of cholesterol to coprosterol are described by Rosenfeld et al. [180]. Although the mode of action of cerebrosides has not been investigated in human beings, Jones et al. [181] have found that serum cholesterol levels can be lowered in man by oral administration of brain cerebrosides.

Thus it is apparent that the intestinal flora may affect serum cholesterol levels in at least two ways, (1) by converting cholesterol to a non-reabsorbable compound, coprosterol, and (2) by degrading bile acids to products which are preferentially excreted in the feces, thus indirectly accelerating the conversion of cholesterol to bile acids. Bersohn et al. [182] have postulated that the intake of cellulose fiber may cause alterations in the bacterial flora as well as increased excretion of fecal fats. In animal husbandry it is well known that the indigestible portion of the feed markedly influences the digestibility of fat, protein and carbohydrate nutrients [183]. Lin et al. [184] have shown in rats that pectin and protopectin markedly affect the excretion of dietary fat but not of endogenous cholesterol. Whether such "bulk" agents have an effect on only intestinal motility and on food-stuff digestibility, or perhaps also on intestinal microorganisms, has not been defined.

We are impressed by the importance of defining (1) the types of intestinal bacteria which flourish in the gut under different feeding conditions and (2) their biochemical capabilities. It will be difficult enough to identify specific changes in flora caused by controlled alterations in dietary intakes in a given patient. It will be much more difficult, but nevertheless illuminating, to define what those bacteria need for their own nourishment, and in turn what they contribute to their host.

TRACE SUBSTANCES

Magnesium. In 1956 Malkiel-Shapiro et al. [185] reported that parenteral administration of magnesium sulfate produced clinical improvement in patients with ischemic heart disease, and reversion of abnormal serum lipoprotein patterns to normal values in many cases. This report was followed in 1957 by a study [186] of serum magnesium levels in Bantu and European South Africans, which purported to show signifi-

cantly higher levels in the Bantu; a correlation in Europeans of serum magnesium and cholesterol levels was strongly negative. It was claimed that the higher the serum cholesterol level, the lower the serum magnesium. In view of the difficulties in making accurate analyses of serum magnesium, it is essential that these findings be independently verified. The clinical claims demand that a double-blind experiment be instituted.

Experimental studies of Vitale et al. [187-188] indicate that magnesium and lipid metabolism may be related, but it is not yet clear whether this relationship is direct or indirect. They have observed that in rats fed a diet containing 10 per cent protein and 24 mg. of magnesium per 100 gm. of diet magnesium deficiency develops *only* when cholesterol and cholic acid are included in the regimen. This was characterized by hyperexcitability, hyperemia of the ears, calcium deposition in the renal tubules, low serum magnesium levels and decreased oxidative phosphorylation of heart muscle mitochondria. All lesions were prevented by raising dietary magnesium four to eightfold. The lipid deposition in the aorta and heart valves caused by the cholesterol and cholic acid loads was greatly reduced when the dietary magnesium was increased, but the elevated serum cholesterol levels rose still further. Increasing the dietary protein intake to 20 per cent decreased the serum cholesterol levels, indicating that the 10 per cent protein intake had been limiting. Clearly, this is a complex phenomenon which deserves further exploration.

Other Metals. Schroeder [189] has presented an interesting postulate based on the abnormal occurrence in tissues of many trace metals (chromium, cadmium, nickel, aluminum, tin and lead). He suggested that these metals might interfere with numerous metal-activated enzyme systems, especially with those dependent on pyridoxine and recalled that this vitamin is involved in the conversion of linoleic to arachidonic acids, and that pyridoxine deficiency in monkeys leads to development of lesions resembling human atheromas. The scheme proposed by Schroeder is ingenious, but to date no direct evidence has been developed. Therapeutic use of metal chelating agents in hypercholesteremia and ischemic heart disease was proposed, but a controlled experimental study by Rosenman and Smith [190] indicated that ethylenediamine tetra-acetic acid (EDTA, or

versene®) when orally administered to rats increased dietary hypercholesteremia only by increasing intestinal absorption of cholesterol. They found no effect on hepatic synthesis of cholesterol, and did not find that it protected against the deposition of fed cholesterol in the liver.

Transitional elements: Curran and Clute [191] showed that the *in vitro* conversion of acetate to cholesterol by liver cell clusters was strongly influenced by vanadium and iron (which depressed it) and chromium and manganese (which increased it). Similar results were obtained *in vitro* in rats [192] and in rabbits [193]. Curran and Costello [193] showed that the regression of aortic lesions in cholesterol-pre-fed rabbits was accelerated by the oral administration of non-toxic amounts of vanadyl sulfate. The site of action of vanadium was localized [194] at the step in cholesterol biosynthesis where the six carbon intermediates are converted to the five carbon precursor (beta-methyl-beta hydroxy glutarate to beta-methyl crotonate); the conversion of mevalonic acid to cholesterol also was inhibited.

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Clinico-pathologic Conference

Primary Hyperparathyroidism, Pancreatitis and Peptic Ulcer

STENOGRAPHIC reports, edited by Lillian Recant, M.D., and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior Medical Students. It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students from the Senior class rather than by members of the faculty.

A WHITE man (retired), sixty years of age, was admitted to Barnes Hospital on November 20, 1956, with the chief complaint of abdominal pain of one day's duration.

The patient had long complained of his health, but had seemed as well as usual until the night before admission. At 9 P.M. severe, steady, non-radiating epigastric pain developed with nausea and vomiting, which persisted essentially unchanged throughout the night. There was no hematemesis or melena. He had had one small bowel movement on the day before admission. Thirty-five years ago, he had been given a diet for duodenal ulcer, with no recurrence of symptoms until three years prior to admission, when he had a bout of similar abdominal pain. He was hospitalized for nine days and treated with nasogastric suction and intravenous fluids. There was no other history of abdominal pain. He drank alcohol occasionally, but not to excess. There was no history of excessive vitamin intake or recent excessive alkali intake.

In the five years preceding admission, the patient had had recurrent attacks of poorly described arthritis and hyperuricemia. The joint pains were controlled by colchicine. He was said to have a fixed low specific gravity of his urine and high blood pressure. He had had a psychotic episode in 1950 treated with electric shock therapy. Many years previously he had had osteomyelitis of the right tibia. Review of other systems and family history were non-contributory.

Physical examination at the time of entry revealed his temperature to be 37°C.; pulse, 80; respirations, 16; blood pressure 180/100 mm.

Hg. The patient was well nourished. He was complaining bitterly of abdominal pain. There was good turgor of the skin but the mucous membranes were dry. The ears, nose and throat were within normal limits. The thyroid gland felt normal. There was an increase in anterior-posterior diameter of the chest. The lungs were clear to percussion and auscultation. The heart was enlarged 2 cm. beyond the mid-clavicular line; the rhythm was regular; there was a grade 2 apical systolic murmur. The abdomen was moderately distended. Guarding was present in the upper part of the abdomen. Liver dullness was normal. No bowel sounds were heard. The rectal examination was normal except for an enlarged prostate. Neurological examination was within normal limits.

The laboratory data were as follows: hemoglobin, 12.8 gm./100 ml.; red blood cell count, 4.36 million per cu. mm.; white blood cell count, 29,350 per cu. mm. with bands, 1 per cent; polymorphonuclear neutrophils, 96 per cent; monocytes, 3 per cent. Red blood cells and platelets appeared normal on stained film of the blood. Urine collected from an indwelling catheter had a specific gravity of 1.011, pH of 5.5; trace of protein; no sugar; many red blood cells and 3 to 5 pus cells were seen in the centrifuged sediment. Repeat urinalyses following the removal of the Foley catheter showed: specific gravity between 1.007 and 1.010; a trace of protein; microscopic examination was consistently normal. The stool benzidine reaction and the blood cardiolipin reaction for syphilis were negative. Blood chemical determinations were as follows: non-protein nitrogen, 33 mg./100 ml.;

TABLE I
SUMMARY OF LABORATORY DATA

Hospital Day	1	2	4	5	7	8	11	14	16	18	21	23	25	28
Amylase (units)	1600	712	100	67	123
Fasting blood sugar (mg./100 ml.)	149	96	103	117	80
Non-protein nitrogen (mg./100 ml.)	28	50	48	72	72	65	59	73	81	64	52	49
Blood urea nitrogen (mg./100 ml.)	46
Uric acid (mg./100 ml.)	9.1	12.7	16.2	18.6	18.6	11.8	9.2
Calcium (mg./100 ml.)	11.9	12.0	11.4	16.9	18.0	16.6	16.3	15.2	14.5	14.6
Phosphorus (mg./100 ml.)	3.0	3.3	4.4	5.8	5.4	5.6	4.5	4.3	3.9
Alkaline phosphatase (Bodansky units)	10.4	4.6
Urinary calcium (mg./day)	169	145	90
Hemoglobin (gm./100 ml.)	12.8	12.8	10.3	9.9	8.3	7.3	9.2	8.5
Transfusion

NOTE: Patient given a low calcium diet on the eighteenth hospital day.

fasting blood sugar, 149 mg./100 ml.; amylase, 1,600 units; uric acid, 9.1 mg./100 ml.; total serum protein, 6.7 gm./100 ml.; with albumin, 5.2; the globulin 1.5 gm./100 ml.; alkaline phosphatase, 10.4 Bodansky units; cephalin cholesterol flocculation, negative; thymol turbidity, 1.5 units; bilirubin, less than 0.8 mg./100 ml. The prothrombin concentration was 100 per cent of normal. The glutamic-oxalacetic transaminase was normal at 11 units. The electrocardiogram was interpreted as questionable old diaphragmatic myocardial infarction. The record was essentially unchanged from one obtained in July, 1950. Roentgenographic examination of the chest was within normal limits. Films of the abdomen revealed multiple air fluid levels and dilated small bowel loops. A small amount of gas was noted in the large bowel.

The patient's hospital course was a complicated one. On admission, he was given nothing by mouth. He received antibiotics and pro-banthine® parenterally as well as demerol® for pain. Fluids were given intravenously. His temperature rose rapidly to between 38° and 39°C. His blood pressure fell gradually to levels of 110/70 mm. Hg and at one time was as low as 98/65 mm. Hg. By the second hospital day, his condition was improved. His abdomen felt softer and bowel sounds were heard. On that day the amylase fell to 712 units. Non-protein nitrogen was 28 mg./100 ml. and the serum electrolytes were as follows; sodium, 150.2; potassium, 3.6; carbon dioxide, 26.3; and chlo-

ride, 112 mEq./L. The serum calcium was 11.9 mg./100 ml.; phosphorus, 3.0 mg./100. By the morning of the fourth hospital day the patient had improved clinically and was started on oral fluids. The blood pressure had returned to the patient's usual somewhat hypertensive levels, but subsequently again fell and averaged 120/70 mm. Hg for the remainder of his hospital course. The amylase had fallen to 100 units, but the non-protein nitrogen had risen to 50 mg./100 ml., despite good urine output. The hemoglobin had fallen to 10.3 gm./100 ml. and the white blood count to 7,050 cells per cu. mm. He began to pass loose stools which were guaiac negative. His temperature fell to normal by the fifth hospital day. However, his non-protein nitrogen continued to rise. (Table I.) He was doing well clinically except for mild nausea and frequent loose bowel movements. Gastric aspiration revealed no free acid. On the seventh hospital day he began having frequent ventricular premature contractions which were controlled by quinidine. A roentgenogram of the chest disclosed infiltration of the left lower lobe. Abdominal films raised the question of osteoblastic metastases in the left ileum. On the eleventh hospital day a firm mass was felt deep in the epigastrium and left upper quadrant. It was non-tender and did not seem to move with respiration. Repeat hemoglobin was 8.3 gm./100 ml. On the fourteenth hospital day blood studies revealed the following: hemoglobin, 8.9/100 ml.; red blood cell count, 2.96 million per cu. mm.;

hematocrit, 29 per cent; mean corpuscular volume, 98 cu. microns; mean corpuscular hemoglobin, 30 $\mu\text{g.}$, mean corpuscular hemoglobin concentration, 30 per cent; reticulocytes, 2.8 per cent; platelets, 920,000. The white count was 17,000 per cu. mm. with basophils, 2 per cent; myelocytes, 4 per cent; metamyelocytes, 3 per cent; band forms, 11 per cent; polymorphonuclear neutrophils, 74 per cent; lymphocytes, 3 per cent; and monocytes, 3 per cent. Moderate anisocytosis was noted on stained film of the blood. The venous pressure was 70 mm. of saline and the arm to tongue circulation time was normal. The patient continued to be quite weak. He was intermittently obtunded and hallucinating. His anorexia continued with occasional nausea. As the serum calcium began to rise (Table 1) the urinary Sulkowitch was 2 plus. Roentgenographic examination of the bones disclosed only dextra-position of the calcified pineal and widening of the proximal right tibia presumably due to old osteomyelitis. There were no cysts and no generalized demineralization. Dental films showed almost complete absence of the lamina dura and coarsening of the trabecular pattern in the alveolar ridges. These changes were thought to be consistent with hyperparathyroidism. An upper gastrointestinal series revealed deformity of the duodenal bulb with an ulcer crater, and what appeared to be extrinsic pressure on the second duodenum thought to arise from the head of the pancreas. On an approximately 200 mg. calcium diet the patient's urine contained between 90 and 167 mg. of calcium per twenty-four hours. An ophthalmological consultant found band keratopathy and bulbar conjunctival deposits of calcium. On the eighteenth hospital day because of rising non-protein nitrogen, an obtunded clinical state, and a moderate relative hypotension of 130/70 mm. Hg, the diagnosis of persistent oligemia was considered. Salt and water were given intravenously with a subsequent fall of the non-protein nitrogen and general clinical improvement. By the twenty-first hospital day, the white blood count had fallen to 9,400 per cu. mm. with a normal differential pattern. On the twenty-fifth hospital day, roentgenographic examination of the chest revealed persistence of infiltration of the left lower lobe. Films of the esophagus showed indentation of the lateral walls near the thoracic inlet. On the thirtieth hospital day, the alkaline phosphatase was 6.1 Bodansky units and the

acid phosphatase 4.6 King-Armstrong units. The non-protein nitrogen was 35 mg./100 ml.; calcium, 15.5 mg./100 ml.; phosphorus, 3.3 mg./100 ml.; sodium, 134.7; potassium, 3.4; carbon dioxide, 30.7; and chloride, 87 mEq./L. The patient continued to vomit intermittently and suffered from postural hypotension. Urinary excretion of 17-ketosteroids was 11.5 mg./day and 17-hydroxycorticosteroids 34.1 mg./day. Repeat determinations the next day were 17-ketosteroids 15.7 mg./day, and 17-hydroxycorticosteroids 48.8 mg./day (interpreted as normal 17-ketosteroids and elevated 17-hydroxysteroids).

The patient was given transfusions until his hemoglobin level was normal and on the thirty-eighth hospital day his neck was explored. A 3 by 2 by 1 cm. purplish mass containing several moderate sized cysts was discovered extending posteriorly from the left inferior pole of the thyroid. The mass was shelled out. Gross and microscopic diagnoses were parathyroid adenoma. A thyroid adenoma was found in the right inferior pole. Postoperatively, while receiving oxygen, the patient became unresponsive. His blood pressure rose to 240/130 mm. Hg and his pulse to 140. Electrocardiogram disclosed intraventricular conduction defect. He seemed to improve markedly when he breathed room air under positive pressure. The blood pressure decreased; the cardiac rate slowed; and the electrocardiogram returned to normal. Urinary Sulkowitch remained 2 plus for the remainder of his life. On the afternoon of the operation, the serum calcium was 17.8 mg./100 ml.; phosphorus, 7.2 mg./100 ml.; carbon dioxide, 28.7 mEq./L.; chloride, 99 mEq./L. On the first postoperative day, the calcium was still 17.6; the phosphorus, 3.9 mg./100 ml. The alkaline phosphatase was 7.9 Bodansky units. On the second postoperative day an auricular flutter developed with a varying block and a ventricular rate of 140 to 170. The flutter continued despite intravenous digitalization. The patient's blood pressure fell. He received norepinephrine, but a short time later his heart ceased to beat. Terminally, 1,000 ml. of dark fluid were aspirated from his stomach. Death occurred on the fortieth hospital day.

CLINICAL DISCUSSION

DR. SOL SHERRY: I should like to begin this conference by asking Mr. Soell to review the specimens removed at surgery.

MR. ERWIN SOEL: The surgical pathologist received three specimens. The first two were thyroid adenomas with a moderate amount of colloid and numerous follicles present. The third specimen was 3 by 1½ by 2 cm. in size, brownish pink in color and had a thin capsule. Section of this specimen revealed numerous small cysts. Microscopic study showed the specimen to be composed of chief cells full of granules and occurring in large sheets. In addition there were a few areas in which vacuolization around the nuclei could be seen. The nuclei were of regular size and no mitotic figures were noted. There was no invasion of the capsule. Only an infrequent large cell with vacuolization of the cytoplasm, characteristic of wasserhelle cells was noted. A diagnosis of parathyroid adenoma was made on the specimen.

DR. SHERRY: Mr. Soell, could this parathyroid adenoma have resulted from chronic renal disease or does its presence imply that we are dealing with primary hyperparathyroidism?

MR. SOELL: The picture is that of primary hyperparathyroidism. At operation, apparently none of the other parathyroid glands was noted to be enlarged, which one would expect in secondary hyperparathyroidism. Primary hyperplasia and hypertrophy would give the picture of wasserhelle cells. The microscopic pathology here was characteristic of an adenoma.

DR. SHERRY: Then we can assume that the patient had primary hyperparathyroidism.

At this time in order to understand more fully the clinical picture presented by our patient, it would perhaps be best to review the pathophysiology of primary hyperparathyroidism. Mrs. Sunseri, what is the current concept of the action of the parathyroid hormone or hormones?

MRS. LINDA SUNSERI: At the present time, it is suggested that there may be two types of parathyroid hormone with different molecular weights. The first of these is believed to have a primary action on bone effecting the mobilization of calcium. As a result an increase in serum calcium and urinary calcium occurs. The second type of parathyroid hormone is thought to act upon the kidney producing a phosphaturic effect, presumably by blocking tubular reabsorption of phosphorus. A recent article by Neuman et al.* deals with certain new concepts of the

mechanism of action of parathormone on bone. They report that parathormone inactivates triphosphopyridine-nucleotide (TPN), an essential coenzyme for the conversion of iso-citric acid to oxalosuccinic acid. Presumably TPN inactivation would also affect other enzymatic processes and would serve, for example, to shunt glucose to pyruvate and citrate by blocking the phosphogluconic system. As a result, citrate accumulation should occur and actually was demonstrated in bone following parathormone administration. It is postulated further that this accumulated citrate forms a soluble calcium-citrate complex which then carries complexed calcium from bone to the serum and tissues. When the citrate moiety is oxidized, free calcium is released. The net effect is an increase in ionized calcium in serum and a removal of calcium from bone.

DR. SHERRY: Mr. Sunseri, what might we expect as the primary major consequences of an excess of parathyroid hormone?

MR. STEPHEN SUNSERI: We would expect an increase in the serum calcium and a depression in serum phosphorus.

DR. SHERRY: Now what other changes might be expected in a patient with excess parathyroid hormone?

MR. SUNSERI: If he had bone involvement, we would expect demineralization of the bone.

DR. SHERRY: What about a third major effect?

MRS. SUNSERI: Renal involvement. This might lead to nephrocalcinosis or stones.

DR. SHERRY: Before we discuss the actual renal lesions, may we say that a third major effect of parathyroid hormone excess would be an increased load of calcium and phosphorus for excretion?

MR. SUNSERI: That is correct.

DR. SHERRY: Let us trace the consequences of each of these three primary effects. Mr. Pakula, what might happen in a patient who had increased bone resorption?

MR. LAURENCE PAKULA: Increased bone resorption might result in decreased bone matrix; in cyst formation; the possibility of giant cell tumors; and spontaneous fractures and bone pain.

DR. SHERRY: Mr. Weiss, are there symptoms or signs referable to the increased level of serum calcium?

MR. LEONARD WEISS: Abnormally high serum calcium levels result in decreased neuromuscular irritability. This is usually manifested by intestinal disturbances with constipation, nausea,

* NEUMAN, W. F., FIRSCHEIN, H., CHEN, P. S., JR., MULRYAN, B. J. and DiSTEFANO, V. On the mechanism of action of parathormone. *J. Am. Chem. Soc.*, 78: 3863, 1956.

TABLE II
CORRELATION OF CLINICAL SYNDROME AND PHYSIOLOGIC DISTURBANCES IN HYPERPARATHYROIDISM

Basic Mechanism	Pathophysiologic Disturbance	Clinical Effects
Increased bone resorption . . .	Deficient bony matrix and cyst formation	Bone pain; osteitis fibrosa, spontaneous fractures, giant cell tumors
High serum calcium and low serum phosphorus	Decreased neuromuscular irritability	Gastrointestinal disturbances (constipation, gastric atony, nausea, vomiting, abdominal pain, muscle weakness and arthralgias, cardiac arrhythmias; electrocardiographic changes (shortened QT interval)
Increased calcium and phosphorus	Calcium deposits in kidneys	Nephrocalcinosis, nephrolithiasis, pyelonephritis (secondary to above)
	Extraskelatal calcification	Band keratopathy, calcification in vessel walls, calcification of various organs, and in connective tissue (lungs, stomach, thyroid, palpebrae, etc.)
Unknown		Neurasthenia and psychoses, peptic ulcer, acute pancreatitis, anemia (secondary to myelofibrosis), polyuria and polydipsia

vomiting and abdominal pain. There may also be generalized weakness, shortened QT interval on electrocardiogram, and the appearance of cardiac arrhythmias. The intestinal disturbance is usually due to atony of the muscles of the gastrointestinal tract.

DR. SHERRY: Miss Stoddard, what might result from the increased load of calcium and phosphorus demanding excretion?

MISS ELIZABETH STODDARD: There would be polyuria followed by polydipsia. The effect on the kidneys, when the overload of calcium becomes too great, may be seen as nephrolithiasis and nephrocalcinosis with final progression to renal failure. Also, we may see extraskelatal calcification in various areas. The latter may appear as calcification in blood vessels, band keratopathy in the eyes, and calcification in various connective tissues.

DR. SHERRY: Are there any organs which are more likely to be involved than others, and if so, why?

MISS STODDARD: Yes, gastric calcification may be frequently found. There is a tendency for the calcium to deposit in areas which are relatively alkaline. The gastric cells which are secreting acid are in such a condition. Also, for similar reasons, calcification may occur in the kidneys and lungs.

DR. SHERRY: Thus, we have developed that

the primary effects of a chronic excess of parathyroid hormone, namely, increased bone resorption, high serum calcium and increased calcium and phosphorus excretion may lead to a variety of clinical alterations.

Mr. Wittmer, are there other phenomena, which may appear in patients with hyperparathyroidism, for which we do not as yet have a good explanation?

MR. JAMES WITTMER: Psychoses and abnormal mental behavior of all types including hallucinations may occur. These are not explainable at this time.

In addition, there are many reports of an increase in the incidence of peptic ulceration. Some investigators claim that the latter is due to an increase in the polysaccharide content of the gastric mucosa but they do not explain how an increase in the mucopolysaccharides leads to ulcers.

There is also an increased incidence of acute pancreatitis. That has been known for some time but has only recently appeared in the literature.* Cope and his associates have a series of cases which suggest that acute pancreatitis is often a preoperative complication of hyperparathyroidism.

* COPE, O., CULVER, T. J., MIXTER, C. G., JR. and NARDI, G. L. Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann. Surg.*, 145: 857, 1957.

DR. SHERRY: To be complete, we should add that anemia may also be observed. This is said to be due to fibrous replacement of the bone marrow when extensive bone disease is present.

Although polyuria and polydipsia may be related to the increased calcium and phosphorus excretion, additional mechanisms, still to be clarified, may be involved.

Our discussion about the effects of a chronic excess of parathyroid hormone are summarized in Table II.

Let us now discuss our patient in greater detail. It will be recalled that at the age of eighteen, he had osteomyelitis; at the age of twenty-five, a diagnosis of duodenal ulcer was made and the patient was given a diet. From the age of twenty-five to fifty-three, the protocol states that he had multiple complaints, suggestive of neurasthenia; a history of polyuria and polydipsia; a urine of fixed low specific gravity, hypertension and a fairly severe constipation. Mr. Rapp, do you think we are justified in suggesting that his hyperparathyroidism has been of very long standing, i.e., that it was present between the ages of twenty-five and fifty-three or perhaps earlier?

MR. EARL RAPP: Yes, I believe that many of the early complaints could have been due to hyperparathyroidism. As Mr. Wittmer pointed out, 10 to 20 per cent of these patients have peptic ulcers in one form or another. Therefore, his disease could have occurred as early as age twenty-five. However, I believe hyperparathyroidism almost surely was present at the time of his acute psychosis at the age of fifty-three. At that time, on admission to McMillan Hospital, there was definite evidence of renal disease.

DR. SHERRY: Then you would suspect that he actually had renal disease for a number of years before his admission to McMillan Hospital with an acute psychosis?

MR. RAPP: I certainly do.

DR. SHERRY: Would you have any explanation for his history of high blood pressure?

MR. RAPP: One can find hypertension in hyperparathyroidism. As was pointed out previously, degenerative vascular lesions may occur secondary to intimal calcification. Perhaps nephrosclerosis and atherosclerosis had developed significantly enough to lead to hypertension.

DR. SHERRY: Would you suspect that his renal lesion was nephrocalcinosis or nephrolithiasis?

MR. RAPP: More likely, nephrocalcinosis was present.

DR. SHERRY: Do patients with nephrocalcinosis also have nephrolithiasis, or does the presence of one usually exclude the presence of the other?

MR. RAPP: Studies indicate that if one type of lesion is present, the other is usually absent.

DR. SHERRY: Yes, that has been reported. One other question, Mr. Rapp. Since the literature is beginning to imply that hyperparathyroidism is more often a chronic disease rather than an acute disease, what is the suspected average duration of hyperparathyroidism in patients in whom the diagnosis is finally established?

MR. RAPP: I cannot give you a definite answer to that but I believe some studies indicate that the disease may have been present for ten to fifteen years.

DR. SHERRY: My recollections are that it is closer to seventeen years on the average, but I would not be surprised if your figures are more correct.

Now in 1953, the patient entered the hospital with an acute psychosis. Mr. Berken, would you comment on the relation of psychoses to hyperparathyroidism?

MR. ARTHUR BERKEN: This relationship has been discussed recently in a review by Bogdonoff and his associates* in *The American Journal of Medicine*. They reported on a case of depressive psychosis which they believe was related to an associated hyperparathyroidism. Since our patient was given electroshock therapy it is quite likely that he too, was suffering from a depressive psychosis. The association of mental disturbances and hyperparathyroidism has been commented on fairly frequently in the recent literature.

DR. SHERRY: What would you guess his serum calcium and phosphorous levels would have been if they had been determined at the time of his acute psychosis?

MR. BERKEN: I believe, as Mr. Rapp does, that hyperparathyroidism was present in this patient at that time. Therefore, he probably would have had an increased serum calcium level, but I am not quite sure of his serum phosphorus level. Although it should have been low, he may have had enough renal damage to make it normal or even slightly elevated.

DR. SHERRY: It may be noted that the urine specific gravity at the time of his admission for

* BOGDONOFF, M. D., WOODS, A. H., WHITE, J. E. and ENGLE, F. L. Hyperparathyroidism. *Am. J. Med.*, 21: 583, 1956.

psychiatric treatment, was 1.003. Why do patients with hyperparathyroidism fix the urine specific gravity at a low level?

MR. BERKEN: In the lesion of nephrocalcinosis, the usual disturbance is a tubular one due to deposition of calcium in the tubular lumens, in the cells of the tubule, and between the cells. This change causes a syndrome of glomerulotubular imbalance, similar to that seen in some cases of chronic glomerulonephritis or pyelonephritis in which one may find functioning glomeruli with malfunctioning tubules. This type of syndrome may account for a continuing diuresis due to excess electrolyte loss and lead to a fixed low specific gravity.

DR. SHERRY: At the age of fifty-five the patient was seen by Dr. Bukantz. At that time the patient complained of multiple arthralgias or arthritis. The serum uric acid level was high but, I believe, Dr. Bukantz noted that the blood urea nitrogen was persistently mildly elevated. Mr. Smathers, do you think that we are justified in accepting the diagnosis of gout in this situation or do you believe these arthralgias also might be associated with hyperparathyroidism?

MR. JOHN SMATHERS: I believe that the patient had gout in addition to hyperparathyroidism, since the uric acid level was elevated to a much greater extent than the blood urea nitrogen. Further, gout may account for his primary renal disease.

DR. SHERRY: Do you think the same way, Mr. Robertson?

MR. PATRICK ROBERTSON: I could not find any connection between hyperuricemia and hyperparathyroidism except as a consequence of renal failure. If we exclude gout, I would not know why he had a hyperuricemia. Of course, there are other conditions that will cause hyperuricemia but there was little evidence for their presence in this patient.

MR. BERKEN: Dr. Sherry, do you know what the serum uric acid level was at the time the patient had his joint complaint?

DR. SHERRY: Dr. Bukantz, can you answer that question?

DR. SAMUEL BUKANTZ: It was about 10 mg. per cent. I would like to point out that the patient had definite articular manifestations, and that he did not have an elevated blood urea nitrogen until four months prior to his admission to the hospital.

DR. SHERRY: Then we shall have to concede that the patient probably had gout. Now at the

age of fifty-seven, he was admitted to a hospital in Europe for severe abdominal pain. He required gastric suction and fluids intravenously during his hospitalization which lasted nine days. The pain subsided and he was discharged. Mr. Beck, what do you believe happened at that particular point?

MR. JAMES BECK: I think that he had either a bout of pancreatitis or an episode of paralytic ileus secondary to his hyperparathyroidism. Either one may be related to hyperparathyroidism and could have been treated successfully with suction; and either one would produce abdominal pain.

DR. SHERRY: In the light of his subsequent course, however, one might suspect that he had a bout of pancreatitis, although the gastrointestinal disturbances of hyperparathyroidism also could have accounted for this episode.

This brings us to the present illness. At the age of sixty, the patient was admitted for the first and only time to Barnes Hospital complaining of severe abdominal pain. It was noted that he had a high amylase and an elevated blood sugar. Would you comment on this part of his course Mr. Spivy?

MR. DIXON SPIVY: I do not think there is any doubt that on admission he was suffering from acute pancreatitis. The clinical findings and laboratory data all support such a diagnosis. In addition, as we have already mentioned, there is a connection between hyperparathyroidism and the pancreatitis.

DR. SHERRY: Was this episode one of acute interstitial or acute hemorrhagic pancreatitis?

MR. SPIVY: Since it was only a moderately severe episode, I do not believe that it was a necrotizing or hemorrhagic pancreatitis.

DR. SHERRY: Mr. Berken, do you disagree with this view point?

MR. BERKEN: I believe in view of the subsequent course that he did have a hemorrhagic pancreatitis.

DR. SHERRY: What data would support your opinion?

MR. BERKEN: The fluctuating non-protein nitrogen level, which was normal when he came in, rose, then dropped before he died. This change would suggest to me the presence of necrosis causing an increased amount of nitrogenous waste to be excreted. Bleeding also could cause a rising non-protein nitrogen level.

DR. SHERRY: Would acute interstitial pancreatitis raise the blood sugar level?

MR. BERKEN: I would guess that elevated sugar levels are only seen with severe pancreatitis.

DR. SHERRY: What significance would you place upon the calcium levels?

MR. BERKEN: We would have anticipated that the patient would have had a high serum calcium on admission. The finding of a normal serum calcium suggests that it was reduced to the normal range by the acute pancreatitis. The reason for the fall in acute pancreatitis is that calcium is said to be bound with fatty acids to form insoluble calcium soaps in areas of fat necrosis. Striking changes in serum calcium often indicate a severe pancreatitis. It is difficult to determine how much the serum calcium fell in our patient.

DR. SHERRY: Mrs. Sunseri, what about the subsequent development of a mass? Is that in favor of hemorrhagic pancreatitis or could a mass be found with acute interstitial pancreatitis?

MRS. SUNSERI: It would be more in favor of hemorrhagic pancreatitis perhaps with the formation of a hemorrhagic cyst. There is another possibility for the development of a palpable mass in the left upper quadrant: the formation of a pancreatic pseudocyst which also may occur following a hemorrhagic pancreatitis.

DR. SHERRY: You would think then that there is strong evidence favoring an acute hemorrhagic pancreatitis or at least a severe pancreatitis with necrosis at the time of admission to the hospital?

MRS. SUNSERI: Yes.

DR. SHERRY: The pain subsided the first two days after admission and the patient appeared to improve. It was noted then that his non-protein nitrogen was rising in spite of a good urine output. The serum calcium was noted to be high normal. The serum phosphorus was noted first to be normal and then subsequently rose. Mr. Weiss, would you like to comment upon the rising non-protein nitrogen?

MR. WEISS: I would say that it was probably due to progressive renal disease.

DR. SHERRY: Do you not think it would be more likely to be related to the acute illness superimposed on the underlying chronic renal disease? We know that his state of hydration was not optimal and that in addition he was hypotensive for a period of time.

MR. BERKEN: The fact that his non-protein nitrogen came down after he was adequately hydrated would support that view.

DR. SHERRY: Fine, then the first two weeks of the patient's hospital admission were concerned with the problems of the acute pancreatitis and its after effects.

Now, during the second part of his hospitalization, that is from the fourteenth to the twenty-eighth day, it was noted that the serum calcium rose to very high levels. However, the urinary Sulkowitch reaction was only 2 plus and the urine calcium was less than 200 mg./day on a low calcium diet. This is somewhat disturbing since patients with hyperparathyroidism usually have a strongly positive Sulkowitch reaction and the twenty-four hour urinary calcium excretion on a low calcium intake will usually exceed 200 mg. Would any of you like to offer an explanation for these findings?

MR. RAPP: Patients with extensive nephrocalcinosis may not excrete increased amounts of calcium in the urine.

DR. SHERRY: Yes, that is a very interesting point which has not been generally appreciated. When extensive nephrocalcinosis develops, the increased calcium excretion is now carried out by the intestine. If one does fecal calcium excretions in patients with advanced nephrocalcinosis, marked increases in fecal calcium are observed whereas early in the course of hyperparathyroidism, almost all the calcium is excreted through the urinary tract.

Mr. Rapp, would you comment on the anemia?

MR. RAPP: The anemia has us all rather confused. We do know that in hyperparathyroidism one may observe an anemia. In this patient, the hemoglobin dropped from 12.8 to 8.3 gm. per cent in a matter of four or five days. That fall would be difficult to explain on the anemia of hyperparathyroidism and would be better explained on the basis of blood loss. Of course, chronic renal disease must also be considered.

DR. SHERRY: This patient's serum calcium level rose to very high levels. At what serum calcium level do we fear parathyroid poisoning and what are its clinical manifestations?

MR. RAPP: I believe the level usually quoted is about 17 mg. per cent. Parathyroid poisoning is believed to be a chemical poisoning due to hypercalcemia. Calcium is rapidly deposited in tissues or organs which are excreting acids such as the kidneys, lungs, stomach, and others. If this condition is not controlled, death may rapidly follow. Acute renal failure may be the first manifestation of parathyroid poisoning and

the latter should be suspected when there is oliguria and a rapidly rising non-protein nitrogen and serum phosphorus level.

DR. SHERRY: Long after our patient's pancreatitis had subsided, he still persisted in having a certain amount of obtundity, anorexia, gastric distention and renal failure. It is quite possible that he was suffering from parathyroid poisoning.

When the patient was sent for a slit lamp examination it was noted that he had deposits of calcium in the bulbar conjunctiva, and he demonstrated band keratopathy. These findings suggested that he had been depositing calcium in the connective tissues for some period of time. Roentgen examination further revealed an absence of the lamina dura. Mr. Robertson, I wonder if you might review briefly the roentgen-rays and comment on the significance of an absence of the lamina dura.

MR. PATRICK ROBERTSON: Chest films taken one week after admission revealed blunting of the costophrenic angles bilaterally suggestive either of fluid or pneumonitis. There was no evidence of bony demineralization. The mediastinum was questionably enlarged. There was some tracheal shift to the right, with elevation and deviation of the left main stem bronchus. These findings were considered to be compatible with a mediastinal effusion, tumor or abscess.

Films of the abdomen, taken on admission, revealed several segments of small bowel filled with air and containing fluid levels, suggestive of ileus.

Spot films of the duodenum during a gastrointestinal examination were interpreted as showing a marked duodenal deformity with a crater at the superior margin. Also there was a suggestion of extrinsic pressure on the second duodenum, possibly by an enlarged pancreas.

Films of the hands did not reveal demineralization, cysts or tumor formation, i.e. the classic features of generalized osteitis fibrosa. However, there was cortical blunting along the margins of the proximal and middle phalanges which is said to be suggestive of hyperparathyroidism. The other long bones were normal.

Films of the skull were normal. Roentgenograms of the mandible revealed a disappearance of the normally present lamina dura. There was also a coarsening of the alveolar bones of the mandible. The disappearance of the lamina dura is important since it is one of the earliest lesions to appear in hyperparathyroidism. The com-

plete absence of the lamina dura about all the teeth in this patient suggests that the process had been going on for some time.

At the level of T₁ to T₃ on barium swallow, a constriction of the esophagus was noted at the thoracic inlet. This finding is compatible with parathyroid or thyroid adenomas.

DR. SHERRY: Mr. Soell, would you comment on the elevated 17-hydroxysteroid excretion in our patient?

MR. SOELL: The degree of elevation appears greater than that which one would expect with a stress reaction secondary to acute illness. My feeling is that there is either hyperplasia of the adrenals or possibly an adrenal adenoma.

DR. SHERRY: You mentioned the possibility of an adrenal adenoma. This patient had a parathyroid and a thyroid adenoma removed at surgery. Could these be related?

MR. SOELL: There have been several cases described with multiple adenomatosis of the endocrine organs. Many of these patients have had a pituitary tumor in association with adenomas of the parathyroid and of the pancreas. However, there have been instances in which no pituitary lesions were found, and there have been cases in which there was nodular hyperplasia of the adrenals in association with a thyroid adenoma. I think this patient may well fit one of these syndromes.

DR. SHERRY: By the time the patient underwent surgery, the diagnosis of hyperparathyroidism was well established. At operation, a 2 cm. parathyroid adenoma and a small thyroid adenoma were found. Mr. Wittmer, would you comment on the relation of serum calcium levels to the size of a parathyroid adenoma?

MR. JAMES WITTMER: Cope* states that if the serum calcium is over 14 mg. per cent and an adenoma, 2 cm. or less, is found at surgery, the patient probably has another adenoma which has been overlooked.

DR. SHERRY: You would suspect in this patient who had a calcium level of well above 14 mg. per cent, and in whom a small parathyroid adenoma was present at surgery, that the chances are excellent that another adenoma was present. Do you believe it probably will be a larger adenoma than the one removed?

MR. WITTMER: I do not know how you could tell. It certainly would be a functioning one.

* COPE, O., ALLEN, J. G., HARKINS, H. N., MOYER, C. A. and RHODES, J. E. *Surgery Principles and Practice*, p. 567. Philadelphia, 1956. J. B. Lippincott.

DR. SHERRY: Mr. Robertson, do you think that the deviation of the trachea in the mediastinum which you demonstrated on the x-ray film could be the site of a large parathyroid adenoma?

MR. ROBERTSON: That is a good possibility since approximately 20 per cent of parathyroid adenomas occur in the mediastinum. They locate there by migrating down with the thymus and may be included in the capsule of the thymus gland.

DR. SHERRY: Do you believe that the subsequent events in this patient support the idea that there is another parathyroid adenoma?

MR. ROBERTSON: Yes, because his serum calcium did not fall.

DR. SHERRY: When surgery is successful, we would expect the serum calcium to fall quite promptly postoperatively and to be at normal levels within a few days. This patient's serum calcium did not fall but was maintained at high levels. Actually it may have been increasing, for the serum calcium taken at the time of death was reported subsequently as 19 mg. per cent.

Now let us turn to the final events. Immediately postoperatively the patient suffered from an episode similar in many respects to that seen with carbon dioxide narcosis. Its relation to the problem of hyperparathyroidism is obscure. On the second postoperative day, an auricular flutter developed. The arrhythmia did not respond to digitalis. Terminally, he became hypotensive and 1 L. of fluid was aspirated from his stomach. Mr. Beck, what do you think the terminal events were due to?

MR. BECK: Probably he died from a cardiac arrhythmia secondary to his high calcium level.

DR. SHERRY: Do you think that gastric dilatation secondary to hypercalcemia also may have occurred?

MR. BECK: Yes, that is possible.

DR. SHERRY: The time has come for us to make a final diagnosis. I believe all the students agree, first, that this patient had a large parathyroid adenoma which will be found in the mediastinum. Second, that he probably died of parathyroid poisoning. Third, he will have extensive nephrocalcinosis.

MR. BECK: Since we did not obtain roentgenographic confirmation of nephrocalcinosis, I believe it should be mentioned that renal dysfunction may occur from high calcium levels without evidence of calcium deposition.

DR. SHERRY: Fourth, the patient will have

areas of increased bone resorption but he will not show the findings of osteitis fibrosa of the generalized type. The frequency of the latter as a manifestation of hyperparathyroidism has been greatly overemphasized in the past. Fifth, we expect to find a subsiding hemorrhagic pancreatitis and possibly an underlying chronic pancreatitis. Additional findings should include a duodenal ulcer; evidence of central lobular liver cell necrosis (because of the protracted shock terminally); and metastatic calcification in vessels and tissues. Finally, the possibility has been raised of multiple adenomas of the endocrine glands.

DISCUSSION BY PATHOLOGIST

DR. FREDERICK T. KRAUS: A moderately firm, oval, lobulated mass (2.5 by 3 by 4.5 cm., 12.0 gm.) was present in the right superior mediastinum adjacent to the esophagus, at the level of the aortic arch. The cut surface was smooth, homogeneous and light brown with two small, round, fluid-filled cysts. Histologic sections (Fig. 1) showed compact masses of uniform small polygonal cells with eosinophilic cytoplasm and round or oval vesicular nuclei and the appearance of parathyroid chief cells. Vascularity was pronounced with numerous capillary channels which in some areas produced a trabecular arrangement. Occasional groups of larger cells with clear cytoplasm were present. Nuclear abnormalities were distinctly uncommon.

The kidneys were of normal size, with mottled red and yellow finely granular cortical surfaces. Fine streaks and granules of gritty yellow material were present in the renal pyramids; there were no stones in the urinary tract. Microscopically the renal tubules showed marked focal degeneration with dark, shrunken cells containing pyknotic nuclei, some of which were encrusted with calcium. Calcium appeared also as casts; in some areas the entire tubule appeared calcified. In places in which tubular rupture had occurred, there was a focal granulomatous inflammatory infiltrate, occasionally with foreign-body giant cells. Most of the calcification occurred in the renal pyramids; however, scattered foci were present in both proximal and distal tubules of the cortex. There was moderate arteriolonephrosclerosis.

Metastatic calcification was not observed in several sections of lung, stomach or basal ganglia.

No large cystic lesions of bone were found;

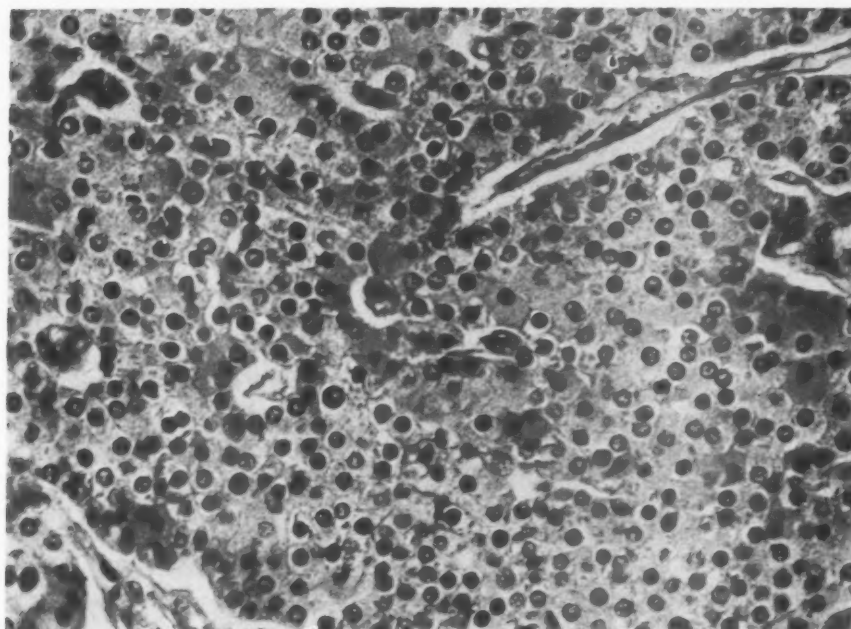


FIG. 1. Section of parathyroid stained with hematoxylin and eosin reveals a rather uniform cell-picture. Note the ratio of oxyphil (dark) cells to chief cells and a few clear cells. Original magnification, $\times 500$.

occasional small focal areas of marrow fibrosis with associated osteoclastic and osteoblastic activity were evident microscopically, however. These osteoclasts appeared to have resorbed large "bites" from the trabeculae; the osteoblasts were rounded up, plump, with a prominent rim of osteoid about the underlying bony spicules.

The pancreas and adjacent fat formed a large, irregular, firm inflammatory mass with many large, soft, pasty, yellow areas of fat necrosis, and small focal hemorrhages. The pancreatic tissues themselves appeared more nearly normal, with only small focal interstitial hemorrhages; the large areas of fat necrosis lay almost entirely in the fat surrounding the pancreas. The main pancreatic ducts were not dilated or occluded, and entered the duodenum through a channel separate from the common bile duct. Histologically, the peripancreatic tissues contained many large areas of necrosis with granular amorphous debris, frequently with foci of calcification. Next was a wide band of fibrosis infiltrated by numerous chronic inflammatory cells and foamy macrophages which stained positively for fat. The regions near the main pancreatic duct showed very little involvement, except for small foci of interstitial fibrosis and infiltrate. Many small and medium sized vessels near the necrotic areas contained old and recent thrombi. There was focal squamous meta-

plasia in some of the smaller ducts associated with inspissation of secretions and acinar atrophy.

No ulcers were seen grossly in the duodenum or stomach; however, microscopic sections of the duodenum did show focal scarring in the lamina propria and Brunner's glands. The overlying epithelium was reconstituted. Acute mucosal ulcers of the esophagus were present and probably explain the altered blood found in the stomach.

The adrenal glands were moderately enlarged (26 cm.). The cortical width varied from 2 to 4 mm. and several small yellow nodules of cortical tissue lie in the capsule. The increase in width appeared to be the result of a widened zona fasciculata microscopically, and the cells of this region were quite foamy with fat-positive vacuoles; focal areas of lipid depletion were also present.

The other endocrine organs were within normal limits. Calcification of ocular tissues was not histologically demonstrable.

Anatomic diagnoses were as follows: Primary: parathyroid adenomas (2) with hyperparathyroidism, one parathyroid adenoma (6 gm.) in the right posterior superior mediastinum, surgical absence of the second parathyroid adenoma (history of removal forty-eight hours prior to death); nephrocalcinosis; hyperparathyroid osteitis fibrosa; extensive focal necrosis of

pancreas and peripancreatic fat necrosis; focal squamous metaplasia of pancreatic ducts; focal cicatrization of pancreas; arteriosclerosis of the aorta, severe and moderate of the coronary cerebral, splenic, mesenteric and renal arteries; arteriolonephrosclerosis, moderate; hypertrophy and dilatation of the heart (500 gm., history of hypertension); old posterior myocardial infarct; acute ulceration of the esophagus; acute cystitis. Accessory: (history of

gout); calcified nodule in the lower lobe of the left lung and a left hilar lymph node; multiple calcified nodules in the liver, spleen and left kidney; focal hyperplasia of the renal tubules; cortical nodular hyperplasia of the adrenals; chronic cholecystitis with cholelithiasis; focal scarring of duodenum and chronic hypertrophic gastritis (history of duodenal peptic ulcer); adenomatous polyp of cecum; diverticulosis of the colon.

Case Reports

Paraldehyde Intoxication with Metabolic Acidosis*

Report of Two Cases, Experimental Data and a Critical Review of the Literature

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PARALDEHYDE was discovered in 1820 by Weidenbusch and fifty-three years later it was introduced into medicine as a hypnotic by Cervello [1]. The compound was thought to be non-toxic by the early workers; however, the first fatal case was reported as early as 1890 [2]. Since that time paraldehyde has grown in popularity as a safe sedative, with periodic enthusiasm for its use as pre-anesthetic medication [3] and obstetrical analgesia [4]; the many fatalities and cases of intoxication have been considered primarily idiosyncratic.

The pharmacology and toxicology of paraldehyde are not completely understood. It is an unstable chemical compound which decomposes to acetaldehyde, acetic acid and probably other compounds. The presence of acetic acid from paraldehyde deterioration has been implicated in four reported deaths. In our studies acetic acid was found to be present in samples of paraldehyde obtained from several hospitals. Severe metabolic acidosis occurred in two patients with paraldehyde intoxication and in a series of dogs fed with deteriorated paraldehyde. The mechanisms of the metabolic acidosis and the identity of the undetermined anions are discussed.

CHEMISTRY OF PARALDEHYDE

General. Paraldehyde is a polyether of cyclic structure with a six-membered ring of three carbon and three oxygen atoms containing no free carbonyl groups. Acidity (U.S.P.) should titrate with not more than 0.5 ml. of 1 N NaOH, using

6 ml. of paraldehyde in 100 ml. of water and with phenolphthalein as indicator. Since paraldehyde may break down to acetaldehyde in light, and further to acetic acid upon oxidation, storage containers should be 4 oz. or less, light-resistant, well-filled and tightly covered [5].

Deterioration of Paraldehyde. Toal's studies revealed that paraldehyde stored two months under varying conditions developed a higher specific gravity, an increase in acidity and content of peroxidized compounds and a higher boiling point [6]. Deterioration increased in proportion to the amount of air space in white glass bottles; small amounts of chemical preservatives and filled amber-glass bottles delayed deterioration. The current U.S.P. [5] and B.P. [7] do not require preservatives and communication with two large drug companies revealed that none are used [8].

Deterioration to Acetic Acid: Cases Reported. Paraldehyde which had deteriorated to acetic acid has been implicated in eight cases of poisoning, including four deaths [9-14]. In three of the fatal cases the drug was administered orally, with death resulting from corrosive changes in the stomach and lungs. The five cases of rectal administration all resulted in painful corrosive burns with one death later from intestinal obstruction.

Analyses of Hospital Paraldehyde. In an attempt to evaluate the incidence of deteriorated paraldehyde in clinical use, various tests were made on fifty-two samples of paraldehyde collected from three Boston hospitals, hereinafter designated

* From I and III (Tufts) Medical Services, Boston City Hospital and Peter Bent Brigham Hospital, Boston, Massachusetts. This investigation has been made with the assistance of a grant from the Committee on Research, Council on Pharmacy and Chemistry, American Medical Association.

† Fellowship sponsored by the American College of Physicians.

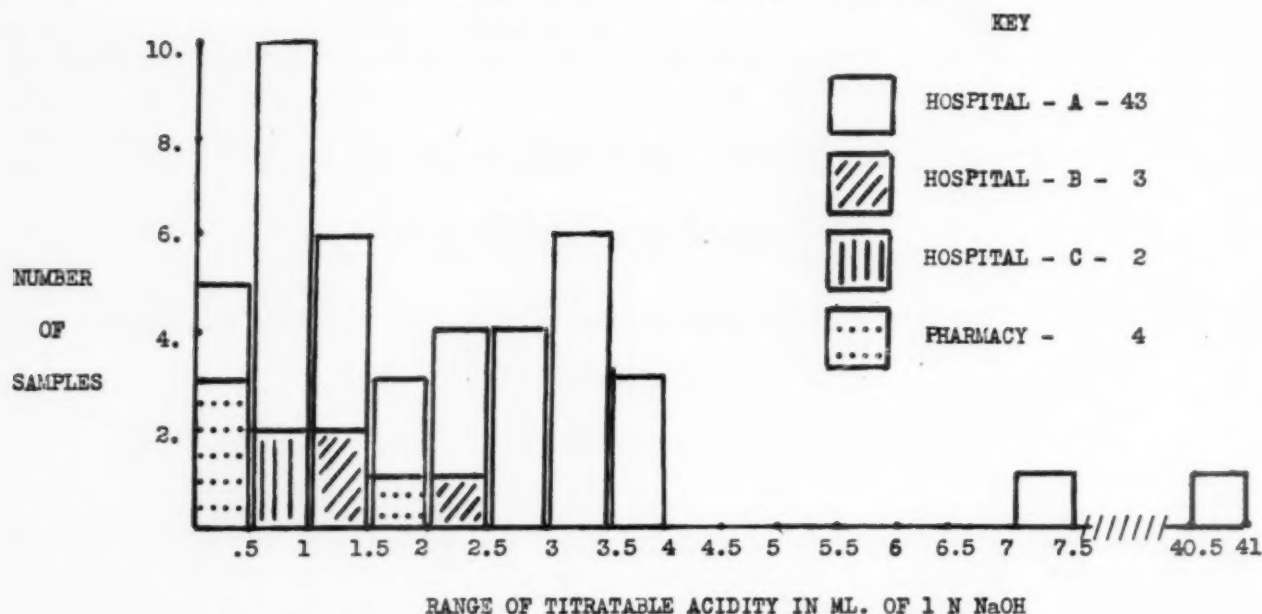


FIG. 1. Paraldehyde samples diagrammed as to range of titratable acidity.

as "A," "B," "C," from several druggists and from standard sealed pharmaceutical products. In hospital "A" forty-two samples from large, white, partially-filled bottles were collected from the wards. Titration with 1 N NaOH to a phenolphthalein end-point required an average of 1.5 ml. 1 N NaOH per 6 ml. of paraldehyde in 100 ml. of water. A sample from hospital "A"'s pharmacy required 0.20 ml. 1 N NaOH. About 11 per cent of the samples were within the U.S.P. standards [5]. A five-year old brown bottle of paraldehyde from the delivery floor required 40.5 ml. 1 N NaOH or was about 40 per cent acetic acid in composition. The average titration by wards in ml. 1 N NaOH was: male medical, 1.87; female medical, 2.03; male surgical, 1.82; female surgical, 1.35; maternity and gynecology, 10.0.

From hospital "B" three samples obtained from partially-filled white bottles required 2.0, 1.45 and 1.3 ml. 1 N NaOH.

From hospital "C" two specimens obtained from nearly full brown bottles aged six months and one month, required 0.90 ml. and 0.55 ml. 1 N NaOH, respectively.

Sterile 5 ml. white ampules required 0.35 ml., while a freshly opened 4 oz. brown bottle required 0.09 ml. 1 N NaOH. Freshly opened paraldehyde, stored in a white bottle 80 per cent full for three months, then required 0.45 ml. 1 N NaOH and tested 1.2 per cent by weight for acetaldehyde (Stratton method). A sample from

a druggist's white 48 oz. half-full bottle required 1.65 ml. of 1 N NaOH and tested 1.6 per cent by weight for acetaldehyde (Stratton method). (Fig. 1.)

These data confirm Toal's findings and the experience of others [6,9-14].

PHARMACOLOGY AND TOXICOLOGY OF PARALDEHYDE

Cardio-respiratory. Carefully controlled and thorough studies on the pharmacologic and toxicologic effects of paraldehyde are few. It was noted early that paraldehyde caused a sizable fall in arterial blood pressure [15]. Sourasky first roughly quantitated the effects of varying doses of rectal paraldehyde used as a preliminary to tonsillectomy in children [16]. With 2 ml. per stone (6.3 kg.) body weight, paraldehyde caused a slight rise in blood pressure; while 4 ml. per stone body weight caused a blood pressure drop for two to three hours, pupillary contraction, depression of respirations and a prolonged deep sleep for eight to eighteen hours. In two other series using multiple drugs in addition to paraldehyde [17,18], it is impossible to estimate the role of paraldehyde in relation to fall in blood pressure. In the latter report shock and cyanosis developed in two cases; a third patient died with asthma and laryngeal tuberculosis [18]. Newborn infants delivered of 100 mothers given paraldehyde had an increased delay of onset of respiratory move-

ment, with one death [19]. The presence of a strong paraldehyde reaction in this dead infant's urine and the close approximation of paraldehyde levels in the cord and maternal blood demonstrated the absence of a significant placental barrier [19,20].

Hepatic. Levine et al., using their vacuum distillation oxidation method for measuring paraldehyde in biological fluids, demonstrated in dogs that the liver plays the major role in the destruction and elimination of paraldehyde, and that the lungs and kidneys excrete less than 31 per cent of the administered dose [21,22]. Bodansky, in suggesting the use of paraldehyde as a liver function test, failed to correlate his studies with standard liver function tests [23]. In two fatal cases of paraldehyde poisoning [24,25], fatty changes in the liver and kidney with toxic hepatitis and nephrosis, respectively, suggest that a toxic decomposition product of paraldehyde may be the offender.

Renal. Two cases of chronic paraldehydism with albuminuria and multiple vitamin deficiencies, with death in one case, suggest possible renal involvement by the drug but scanty laboratory and postmortem data limit the value of the report [26]. In a patient treated with low dosage of paraldehyde (24 ml.) during labor metabolic acidosis and albuminuria developed [27].

Metabolic. A masterly early study of the metabolic effects of paraldehyde given orally to dogs by Pawel demonstrated that sleep-producing doses, 0.43 gm./kg., caused mild hypoglycemia; while narcotizing doses, 2.3 gm./kg., produced marked hyperglycemia, glycosuria, hypothermia and increased nitrogen excretion in the urine [28]. Hitchcock, although unable to measure acetaldehyde in the expired air from mice with damage to the liver from carbon tetrachloride and heavy paraldehyde intoxication, proved the availability of paraldehyde as a precursor of acetyl groups for the acetylation of sulfanilamide in the urine of mice [29,30]. These results supported the hypothesis that paraldehyde is depolymerized to acetaldehyde which is then oxidized to acetic acid. The acetic acid thus formed may then be metabolized to carbon dioxide and water via the citric acid cycle, if oxaloacetate and coenzyme A and adenosine-triphosphate are available. The acetate may also be used in the synthesis of fatty acids or of glucose and glycogen. If the requirements for the normal disposition of acetate are not present,

the acetate may pool in the blood and contribute to a metabolic acidosis. In the course of investigating the bisulfite-binding power, a measure of carbonyl compounds, Taylor et al. found three instances of a rise in carbonyl compounds when high dosages of paraldehyde or chloral hydrate had been given [31]. This suggests that paraldehyde, with no free carbonyl group, is broken down to a compound with free carbonyl groups, i.e., acetaldehyde. Mendelson et al., in studying the effect of narcotics on coenzyme A activity, found that paraldehyde did not interfere with acetylation in their system [32]. Mice and dogs treated with tetraethylthiuram disulfide (antabuse®) by Keplinger and Wells showed higher and more prolonged blood levels of paraldehyde and acetaldehyde than did normal animals [33]. Acetaldehyde is presumed to be oxidized *in vivo* by aldehyde dehydrogenase which tetraethylthiuram disulfide is known to inhibit.

Tolerance. Chronic paraldehydism, with the development of tolerance and the symptoms of tremulousness, restlessness, mental anxiety and agitation, was first noted by Hartz [15]. Tolerance, produced experimentally in adult guinea pigs with twelve tri-weekly intraperitoneal injections of paraldehyde, delayed the onset and shortened the duration of sleep, and shortened the total hypnosis [34]. Chapman mentions the development of tolerance, substitution for alcohol and chronic addiction to paraldehyde in alcoholics [35].

Parenteral Administration. Burstein demonstrated in human subjects and in animals that intravenously administered paraldehyde is extremely hazardous, leaving a very narrow margin between the minimal anesthetic and the minimal lethal dose. Slow intravenous infusion of paraldehyde causes apnea for seconds, rapid shallow respirations, coughing, cyanosis, hypotension, tachycardia and death within minutes from massive diffuse pulmonary hemorrhage and dilatation of the right side of the heart; or death within hours due to the development of pulmonary edema [36,37].

Johnson first reported the intramuscular use of paraldehyde therapeutically in twenty patients with intractable pain, convulsions or disturbed mental state [38]. He recognized the highly irritating effects of paraldehyde and recommended giving the injections deep in the buttocks to avoid sloughing the skin. But ten years later Woodson reported three cases of

severe and permanent sciatic nerve injury caused by deep intramuscular injection of paraldehyde [39]. Several additional unpublished instances of skin slough and sterile abscess of the buttocks, as well as another case of sciatic nerve damage, have come to our attention.

These reactions are readily understandable in light of the instability of paraldehyde and possible contamination with acetic acid or acetaldehyde; therefore, parenteral use of this drug should in general be avoided.

Other Reported Cases of Toxicity in the Literature. In addition to those previously mentioned, the literature contains four fatal cases and eleven non-fatal cases of paraldehyde toxicity [40-46]. The use of benzyl alcohol as a local anesthetic with rectal paraldehyde probably added to the incidence of reactions [47].

Reported Deaths from Paraldehyde. Besides those already mentioned the surveys by Alexander et al. and Moore et al. of deaths from poisoning in Massachusetts report twenty-two cases of paraldehyde death from 1928 to 1948 [48,49].

The introduction of the spectrophotometric semicarbazide method for measurement of acetaldehyde in body fluids by Burbridge et al. in 1950 [50], and the modification of the method for measuring blood and tissue paraldehyde by Figot et al. in 1952 [51] and by Stratton in 1953 [52] have provided a recent impetus for studies of the pharmacology and toxicology of paraldehyde. Figot et al. established the lethal blood:brain ratio in rats and reported a series of four paraldehyde deaths with blood level measurements ranging from 54 to 148 mg. per cent of paraldehyde [51]. In Stratton's series of medical examiner's cases there were nineteen deaths attributed to paraldehyde, with a range of blood levels from 49 to 160 mg. per cent of paraldehyde, and a postulated minimal lethal level at about 50 mg. per cent of paraldehyde [53].

Unreported Deaths from Paraldehyde. The following data are the preliminary and incomplete results of a survey of deaths from paraldehyde in the United States.

An analysis of eighty-three cases of paraldehyde intoxication and/or addiction from the Boston City Hospital for the years 1931 to 1946 showed three deaths attributable to paraldehyde.

A survey of coroners and medical examiners in the major cities of the United States concerning paraldehyde deaths has at present resulted in twenty-five replies: sixteen agencies reported no

deaths due to paraldehyde; the nine positive replies accounted for thirty-one deaths caused by paraldehyde since 1950.

To our knowledge, there has been a total of ninety-three deaths from paraldehyde in the sixty-four years of its clinical use as a sedative. In viewing the reported deaths by fifty-year periods, it is apparent that there has been a recent increase in the incidence of deaths. From 1882 to 1900 two deaths were reported; from 1900 to 1950, thirty-one deaths; from 1950 to 1956, sixty deaths. Much of the earlier failure to recognize this drug as a cause of death probably lay in the lack of methods of measurement and also in the lack of recognition of its toxicity. Another probable factor was the inefficiency of the old coroner system as contrasted with the relatively recent medical examiner system of medico-legal investigation with modern laboratory facilities. The fact that, even today, most coroners' and medical examiners' reports do not reach the medical literature also prevents a true evaluation of the role of paraldehyde as a toxic agent.

CASE REPORTS

Metabolic Acidosis in Two Paraldehyde Addicts

CASE 1. L. H. (M.G.H.).* This forty-three year old former nurse entered the hospital in May, 1954 because of vomiting of brownish material. The patient had been a severe psychiatric problem for fifteen years, with antisocial behavior characterized by temper tantrums, pathologic lying and chronic addiction to morphine, barbiturates, paraldehyde and benzedrine.® In 1942 she spent several months in a mental hospital for morphine addiction. In 1948, after taking six bichloride of mercury tablets in a suicidal attempt, she recovered with only mild pharyngitis, gastroenteritis and mild renal damage manifested by transient (four days) 4-plus albuminuria, microscopic hematuria, fixed specific gravity of the urine and polyuria. During three other hospital admissions the patient required large doses of barbiturates, paraldehyde and opiates. Antisocial behavior, diarrhea and seven pounds weight loss were the presenting problems in the first 1954 admission. After appropriate examination, hepatomegaly and psychoneurosis were found and fifteen 8 ml. doses of paraldehyde were given in eight days. Following discharge the patient received six weeks of psychotherapy; medication included nightly doses of 0.6 to 1 gm. of nembutal,® 25 to 30 ml. of paraldehyde and morning doses of benzedrine. On this regimen she stopped drinking

* This case report was made available through the courtesy of Dr. Alfred Kranes of the Massachusetts General Hospital.

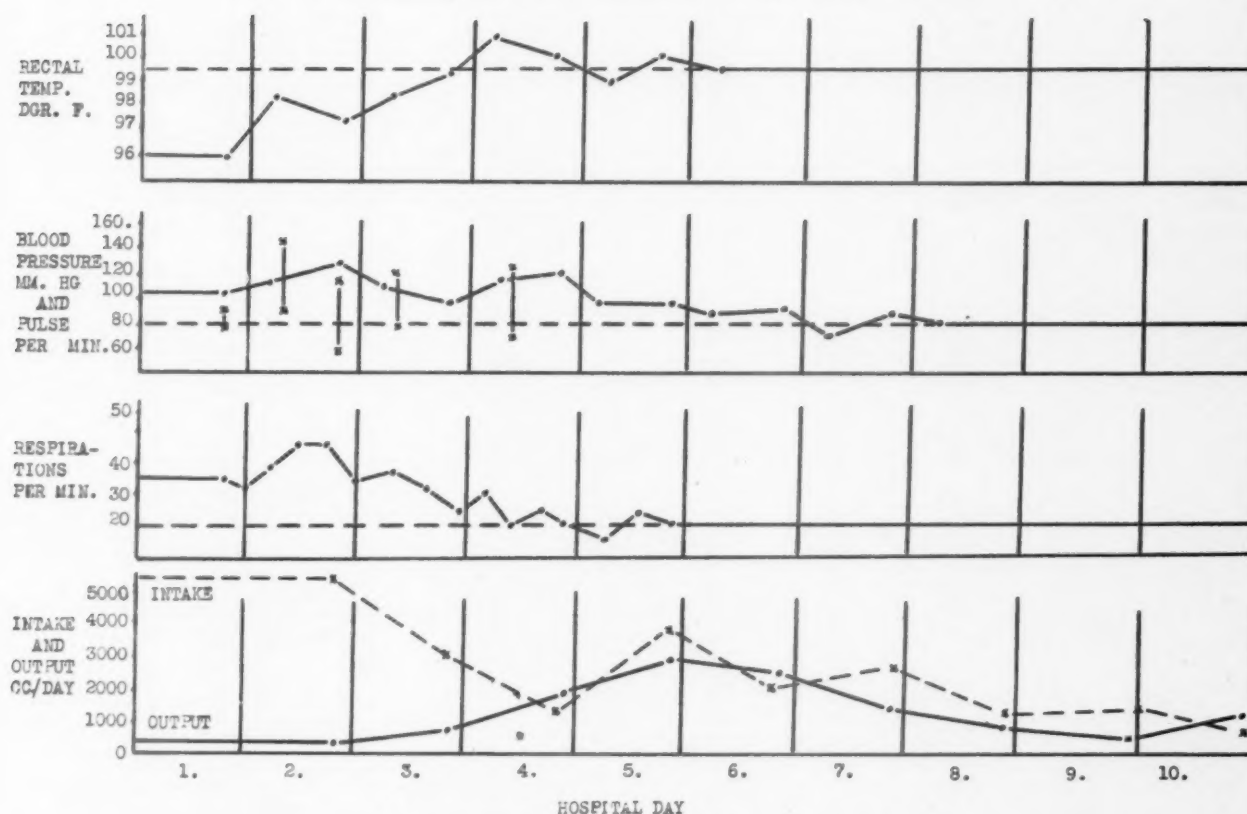


FIG. 2. L. H. Vital signs and intake and output.

alcohol, had fewer temper tantrums and had less diarrhea, but remained antisocial with poor appetite and an additional seven pound weight loss. Two days before the present admission the patient obtained a 120 ml. bottle of paraldehyde. That evening, after drinking part of this paraldehyde, she vomited and the following morning had a blood-tinged emesis. Drowsiness, inability to eat more than breakfast were noted on the day before admission when she consumed the remainder of the paraldehyde. On the day of admission drowsiness, vomiting of coffee grounds material, anorexia, abdominal and mid-back pain were present. Demerol,[®] 300 mg., was administered subcutaneously over a four-hour period just prior to admission. The persistent emesis of brownish material prompted admission at 10 P.M.

On examination the blood pressure was 90 systolic and 80 diastolic mm. Hg; apical pulse, 100 per minute; respirations, 36 per minute; rectal temperature, 96°F.; and weight, 100 pounds. The patient, a thin, dehydrated white woman with a brownish discoloration of the skin, was oriented, anxious, tremulous and had a sallow blotchy cyanosis distributed over pulseless cool arms and legs.

The pupils were small, reacting normally to light, and the extraocular movements were jerky. The tongue was dry and tremulous, the teeth in poor repair. The odor of paraldehyde was present. Examination of the heart revealed a systolic gallop. The lungs were clear. Slight abdominal distention with

diffuse resistance to palpation was not accompanied by rebound or localized tenderness. The liver was enlarged to 6 cm. below the right costal margin and was tender to percussion. Rectal examination yielded no feces.

Figure 2 outlines the vital signs, and intake and output. Table 1 lists the laboratory data during the hospital course.

One hour after admission 1,000 ml. of thick brown guaiac-positive gastric contents were aspirated. A catheterized urine specimen at this time revealed a specific gravity of 1.030, 1-plus albuminuria, 1-plus sugar, no acetone and some hyaline casts. A white blood cell count was 65,400 per cu. mm. The following morning the blood pressure was normal, pulse feeble, hands still cool and cyanotic, and the patient was confused and jittery. Barbiturate-withdrawal syndrome was considered, and sodium phenobarbital was given, with little effect. That evening the patient's general appearance was poor, with twitching, incoherence of speech, cyanosis and vascular collapse. Tachycardia and marked air hunger persisted. After intake of 5,500 ml. of intravenous fluids, only 475 ml. of acid urine had been collected. The urine showed persistent 1-plus glycosuria and albuminuria. The initial difficulty in obtaining venous blood was overcome after intravenous replacement of blood volume. The blood studies revealed a metabolic acidosis. Alkalinizing therapy was begun.

On the morning of the third day the patient had

TABLE I
CASE I, LABORATORY RESULTS

Hospital Day	Non-protein Nitrogen (mg. %)	Carbon Dioxide Combining Power (mM/L.)	Serum Chloride (mEq./L.)	Serum Sodium (mEq./L.)	Serum Potassium (mEq./L.)	pH Venous Blood	Hematocrit (%)	Total White Cell Count (cu. mm.)	Urine Specific Gravity	Urine Sugar	Urine Albumin
2	48	9.0	108	133	5.5	46	47,400	1.030	1 +	1 +
3	66	10.5	96	127	5.0	7.28	44	34,900	1.030	1 +	0
4	36	14.0	100	132	3.4	14,700	1.018	0	0

good color but was delirious. Respirations continued deep and rapid. That evening she was drowsy, confused and had gastric distention with persistence of tender hepatomegaly and air hunger. Intravenous fluid intake totaled 3,120 ml. and urinary output was about 800 ml. The venous blood pH without stasis was 7.28. The serum inorganic phosphorus was 2.6 mg. per cent.

On the fourth hospital day the temperature rose to 101°F. and basilar rales appeared. Penicillin administration was started. Subsequently the patient's mental and physical status improved rapidly, vital signs returning to normal and output equalling intake. She was discharged on the eleventh hospital day. In a subsequent hospital admission in December, 1954, the patient entered for evaluation of convulsions. The electroencephalogram was mildly and diffusely abnormal; blood and urine studies were normal.

CASE II. P. F. (B.C.H. and P.B.B.H.). This thirty-eight year old man, a divorced, unemployed laborer, entered the hospital in February, 1956 because of bloody vomitus. From the ages of sixteen to thirty-two the patient's alcoholism and gambling resulted in an unsuccessful record in school, the army and in marriage. After paraldehyde treatment for alcoholic withdrawal symptoms, the patient became addicted to paraldehyde about five years prior to hospital admission. Since then he had consumed at least 150 to 300 ml. of paraldehyde a week, along with varying amounts of barbiturates and alcohol. To obtain these amounts of paraldehyde he kept several different doctors "on the string."

In 1952 and 1953 he spent several days each year in the hospital for alcoholic tremulousness. He made six visits, each of three weeks' duration, to a rural Alcoholics Anonymous camp without rehabilitation. On several occasions the patient had convulsions with attempted withdrawal and became extremely fearful of stopping his multiple addictions. In the fall of 1955 he spent ten days in a chronic disease hospital for alcoholics where he had several convulsions with as-

sociated head trauma and burns from a radiator. In early February 1956 the patient was admitted to the overnight ward of a hospital because of shakiness and was there given some paraldehyde. During these five years of multiple addictions the patient lost forty pounds and had an extremely poor dietary intake.

During the five days prior to hospitalization, the patient drank about 360 ml. of paraldehyde and an undetermined amount of wine, whiskey and beer. Three days before admission the patient was observed by his family to have acquired an unlabeled 120 ml. brown bottle of paraldehyde from a source other than the usual druggists. He drank about 60 ml. of this paraldehyde on the same day and soon appeared drowsy, listless and ataxic with labored breathing, a throat rattle and much coughing. He remained at home in bed and continued to consume 8 to 15 ml. doses of this and other paraldehyde until it was gone. His symptoms worsened, he became weaker, more deeply stuporous and began to vomit. The evening before admission red blood was observed in the brown vomitus and he was admitted at 11 A.M. the next day.

No history of ingestion of methyl alcohol, antifreeze or antabuse in the days before admission could be obtained. Jaundice and disease of the liver were denied.

On examination the blood pressure was 80 systolic and 0 diastolic in mm. Hg; apical pulse, 120 per minute; respirations, 40 per minute; and temperature, 98.6°F. rectally. The general appearance of the patient was that of a moderately stuporous, sick-looking, thin, dehydrated white man. Peripheral pulses were not palpable, the extremities were cool. The patient was oriented. His air hunger was striking. A strong odor of paraldehyde filled the room. The skin was dry, smooth, with poor turgor. The eyeballs were sunken, sclerae white, pupils equal but sluggish in reaction to light, and the fundi were normal. The heart sounds were distant and of poor quality. The lungs had scattered rhonchi with a tracheal rattle. The liver was percussed to 3 cm. below the right costal margin. There was marked epigastric rigidity, tenderness and voluntary spasm. All skeletal muscles

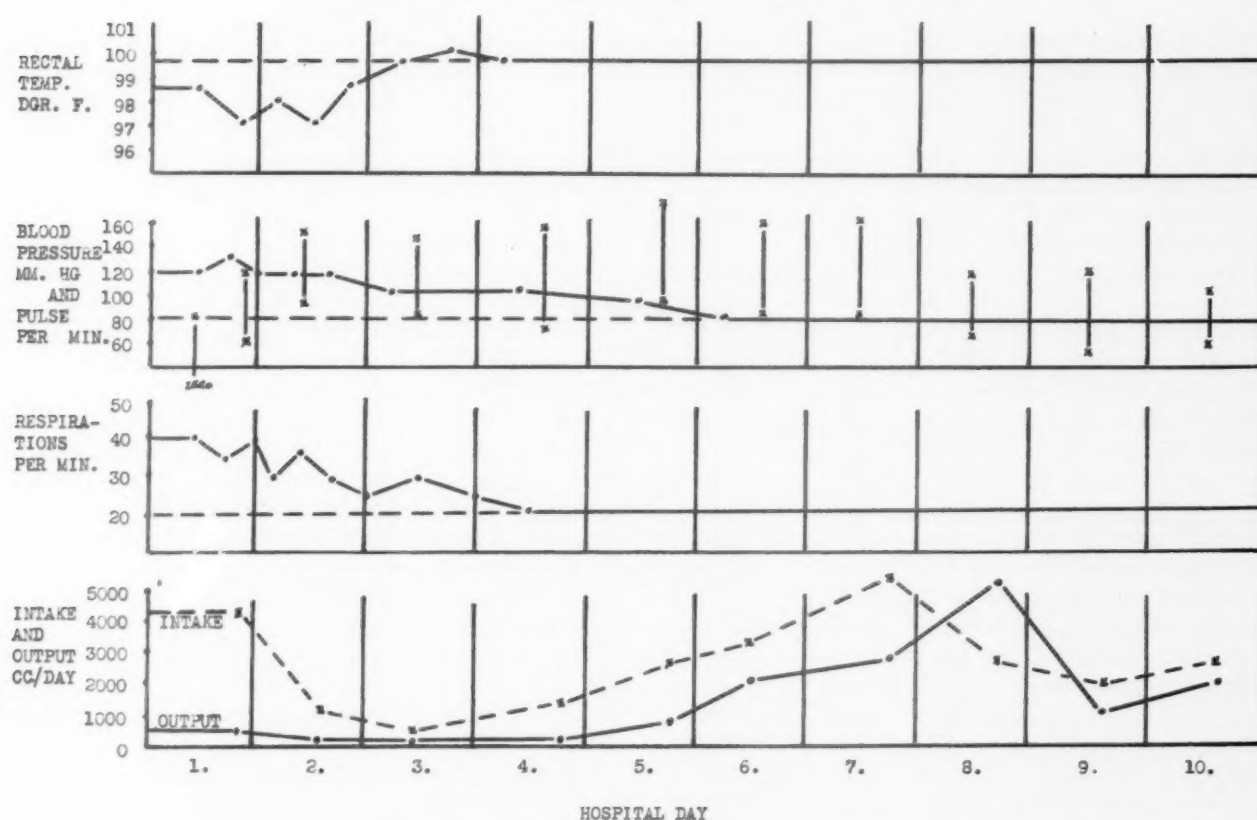


FIG. 3. P. F. Vital signs and intake and output.

manifested asynchronous coarse twitching, accentuated by direct percussion. Chvostek's sign was present but carpopedal spasm and Trousseau's sign were absent. Rectal examination revealed soft, brown, guaiac-negative feces. Neurologic examination revealed depressed sensorium, muscular irritability, generalized weakness and absent deep tendon reflexes in the legs.

Figure 3 outlines the vital signs, and intake and output. Table II lists the laboratory data during the hospital course.

The initial hypotension was quickly remedied with intravenous infusions of saline solution. The clinical picture appeared to be that of a dehydrated, starved, chronic alcoholic with moderate paraldehyde narcosis, but blood chemical studies made on admission and elevated plasma ketones (2-plus qualitative) suggested diabetic acidosis. However, 150 units of crystalline zinc insulin given subcutaneously led to hypoglycemia in two hours. The initial urine was obtained by catheter twelve hours after admission and revealed a pH of 5, specific gravity of 1.018, 2-plus albumin, 2-plus sugar, no acetone and a sediment of two to three red cells, five to eight white cells and three to five wide hyaline and granular casts per high power field, with several renal tubular epithelial cells.

The next morning the patient remained stuporous, with continued marked air hunger. He experienced

several episodes of cyanosis and coarse rattling of tracheal secretions which necessitated an airway and tracheal suction. A lumbar puncture revealed clear fluid under low pressure with five red cells, negative Pandy test and 4-plus qualitative aldehyde test (Schiff). Gastric aspiration yielded 300 ml. of thick black material which was 4-plus guaiac and negative for salicylates (ferric chloride test). The clinical condition of the patient failed to improve; chemical determination showed only a drop in potassium despite infusion of 50 per cent sodium bicarbonate; a venous blood pH, with minimal stasis, was 6.89. Initial toxicologic studies revealed a high level of paraldehyde in the blood and no demonstrable methyl alcohol or formic acid. No oxalate crystals were found in the urine. In the face of virtual anuria and the necessary high intake of base to reverse the severe acidosis, further intravenous therapy was considered detrimental to the patient because of the inevitable hypervolemia and its effects.

After twenty-eight hours at Boston City Hospital the patient was transferred to the Peter Bent Brigham Hospital and on the evening of that day was dialyzed by means of the artificial kidney for three and a half hours. The arterial blood pH rose from 7.01 units predialysis to 7.23 postdialysis. Anuria persisted for two days, during which time the patient was obtunded, confused and tremulous; on the third hospital day he had a grand mal seizure. During the first week the

TABLE II
CASE II, LABORATORY RESULTS

Hospital Day and Hours after Adm.	Non-protein or Blood Urea Nitrogen (mg/100 ml.)	Carbon Dioxide Combining Power (mM/L.)	Serum Chloride (mEq/L.)	Serum Sodium (mEq/L.)	Serum Potassium (mEq/L.)	pH Blood	Blood Sugar (mg/100 ml.)	Serum Calcium (mg/100 ml.)	Serum or Urine Paraldehyde* (mg/100 ml.)	Serum or Urine Acetaldehyde* (mg/100 ml.)	Lactate† (mEq/L. serum H ₂ O)	Pyruvate† (mEq/L. serum H ₂ O)	α -keto-glutarate† (mEq/L. serum H ₂ O)	Hematocrit (%)	Total White Blood Cell Count (cu. mm.)	Urine Specific Gravity	Urine pH	Urine Sugar	Urine Ketones	Urine Albumin	Stool Guaiac
1 Adm.	N.P.N. 32	12.1	101	135	8.8	240	11.7	Serum 101	Serum 10.6	54	26,000	0
2 14 hr.	49	<5.0	101	138	6.3	116	...	Urine 57	Urine 5.8	1.018	5.0	2+	0	2+	...
2 21 hr	54	<5.0	100	138	6.5	Venous 6.89	Serum 26.8	Serum 4.0	1.97	0.125	0.035	42	29,000	0
2 30 hr.	B.U.N. 55	8.4	93	143	6.8	Arterial 7.01	71	15.6	43	0
Dialysis 3	35	10.9	96	135	3.8	7.23	107	37	6.5	2+	0	1+	1+
6	75	25.8	95	130	3.2	114	9.4	30	4.5	0	0	±	3+
9	36	21.8	95	134	3.8	83	32	10,150	1.006	7.5	0	0	±	1+

* Stratton method [53].

† Hucklebee method [54].

patient had guaiac-positive stools and a drop in hematocrit. X-ray studies of the upper gastrointestinal tract were normal. Liver function studies revealed a total serum bilirubin of 0.8 mg. per cent, the cephalin flocculation test was negative; formol gel test, 4-plus; prothrombin time, 80 per cent; bromsulfthalein, 3 mg. per cent retention in forty-five minutes; total serum protein, 5.0 gm. per cent; albumin, 4.0 gm. per cent; serum alkaline phosphatase, 10.3 Bodansky units; inorganic phosphorus, 1.3 mg. per cent; total cholesterol, 143 mg. per cent. A standard (100 gm.) oral glucose tolerance test gave the following glucose levels: fasting, 83 mg. per cent; one-half hour, 143 mg. per cent; one hour, 125 mg. per cent; two hours, 46 mg. per cent; three hours, 70 mg. per cent; four hours, 70 mg. per cent. Serum amylase was 800 units, later 234 units. The bleeding time was four and a half minutes; clotting time, eight and a half minutes. A film of the chest showed the heart and lungs to be normal. Serial electrocardiograms revealed high peaked T waves in the precordial leads, with lowering of T waves to normal on the seventh hospital day.

After the upper gastrointestinal bleeding (due to gastritis) and the dysuria and tenderness of the testicles (due to acute prostatitis and epididymitis) had cleared, the patient gradually became more alert and stronger. The blood studies reverted to normal. He was discharged on the thirty-fourth hospital day.

DOG EXPERIMENTS

The general procedure used was a modification of that described by Levine et al. [27]. Baseline studies were obtained on venous blood, and paraldehyde of varying acidity was administered by gastric tube until narcosis and finally death occurred. During the narcosis a femoral arterial cannula was inserted under local anesthesia and a Touhy adapter attached.

Arterial samples were collected in heparinized air-free syringes for pH, pyruvate and lactate determinations, the pH values being measured immediately by means of a portable Cambridge pH meter.* Pyruvate and lactate were determined by the method of Huckabee† [54]. Arterial blood for routine chemical study was collected and the separated serum overlaid with mineral oil. Arterial blood for estimation of paraldehyde and acetaldehyde was collected in double-oxalated vacuum tubes overlaid with mineral oil, and the values determined by the Stratton method‡ [53].

Three dogs were studied. Each dog received

paraldehyde (1.30)§ every three hours until six doses had been given. After the first arterial blood samples were taken at 12 noon, dog 1 received paraldehyde (2.30)§ every one and a half hours for eight doses. Dogs 2 and 3 received one additional dose of paraldehyde (1.30).§ The femoral cannula insertion caused much excitement in dogs 1 and 3. Blood samples were taken from each dog, and successive doses of paraldehyde were administered at the times indicated in Table III.

In dog 1, a thin, young 20.5 kg. female, respirations ceased at 11:16 P.M. and the heart stopped at 11:20 P.M. Total time to death was twenty-eight hours and thirty minutes. Estimated total blood loss was 275 ml., with replacement of 750 ml. of intravenous fluids. Total paraldehyde administered was 108 ml., or about 5 ml./kg. and about 3.8 ml./hour.

In dog 2, a young, muscular 16 kg. male, respirations stopped at 4:35 P.M. and the heart stopped at 4:40 P.M. Total time to death was twenty-one hours and forty minutes. Estimated total blood loss was 180 ml., with replacement of 75 ml. of intravenous fluids. Total paraldehyde given was 63 ml., or about 4 ml./kg. and about 2.8 ml./hour.

In dog 3, an old, fat 16 kg. male, respirations ceased at 3 P.M. and the heart stopped at 3:05 P.M. Total time to death was nineteen hours and fifty minutes. Estimated total blood loss was 150 ml., with replacement of 50 ml. of intravenous fluids. Total paraldehyde administered was 35 ml., or about 2 ml./kg. and about 1.8 ml./hour.

RESULTS

It will be noted in Table III that all dogs had a reduction in the bicarbonate reserve during the experiment and that a very low pH was obtained in one case. A lacticacidemia present in the three dogs was poorly correlated with excitement at the time of cannulation and had a tendency to drop terminally in the last two dogs. In all dogs varying degrees of glycosuria developed. The serum chlorides tended to be high and all the paraldehyde levels terminally were above 119 mg. per cent.

During the first twelve hours the dogs progressed from ataxia to sleep and coma. In dog 1 extreme hyperpnea developed at 4:45 P.M., with deep sighing respirations at a rate of 80. This continued until 9 P.M. when a bag placed over its head caused a quieting of the breathing. It is of interest that serial serum lactate and pyruvate levels during the process of death showed no marked change in dog 1. In dogs 2 and 3 thick reddish-yellow foam poured from the mouth and

§ In parentheses after each dose of paraldehyde is the titratable acidity in ml. 1 N NaOH.

* pH readings and blood chemical studies were obtained through the courtesy of the Veterans Administration Hospital (W. Roxbury) Research Laboratory.

† Pyruvate and lactate studies were made through the courtesy of Dr. William Huckabee of the Massachusetts Memorial Hospital.

‡ Paraldehyde/acetaldehyde studies were made through the courtesy of Mr. Frank Stratton of the Medical Examiners' Service, Suffolk County.

TABLE III
 LABORATORY RESULTS OF DOG EXPERIMENTS

Dog Number	Date	Hour	Carbon Dioxide Combining Power (mM/L.)	Serum Chloride (mEq./L.)	Serum Sodium (mEq./L.)	Serum Potassium (mEq./L.)	pH Arterial Blood	Whole Blood Paraldehyde (mg./100 ml.)	Whole Blood Acetaldehyde (mg./100 ml.)	Lactate (mEq./L. Blood H ₂ O)	Pyruvate (mEq./L. Blood H ₂ O)	Comment
1	5-31-56	6:30 P.M.	20.5	116.5	143	5.4	0.5	3.3	Control
	6-1-56	12 N	16.3	114.7	143	4.6	7.62	73.9	2.4	8.197 7.723	0.165 0.174	After 36 ml. paraldehyde
		5 P.M.	15	115.6	143	3.9	119.3	2.2	After 58 ml. paraldehyde
		5:30 P.M.	13.6	115.6	141.6	3.6	116.8	1.9	After 58 ml. paraldehyde
		5:45 P.M.	13.2	121	141.6	3.6	121	1.4	After 58 ml. paraldehyde
		6 P.M.	15	121	143	4.0	7.59	98.8	3.1	3.100 2.023	0.160 0.133	After 58 ml. paraldehyde
		6:20 P.M.	10.9	112	135.9	...	7.59	After 68 ml. paraldehyde
		7:45 P.M.	7.57	After 68 ml. paraldehyde
		9:15 P.M.	7.52	After 88 ml. paraldehyde
		10:15 P.M.	7.52	After 98 ml. paraldehyde
		11:17 P.M.	15.9	102	135.9	4.9	7.18	210	2.5	7.070 7.127	0.139 0.108	After 108 ml. paraldehyde
		11:22 P.M.	16.1	101	138.7	4.9	7.746 6.018	0.166 0.142	After 108 ml. paraldehyde
		11:25 P.M.	7.18	8.804 5.224	0.205 0.146	After 108 ml. paraldehyde
2	5-31-56	7 P.M.	19	116.5	1.3	2.4	Control
	6-1-56	12 N	12	121	147.3	5.6	7.49	102.9	1.8	10.535 13.613	0.180 0.188	After 43 ml. paraldehyde
		3:45 P.M.	13.6	122.8	150.1	5.5	107.9	1.5	5.744 4.692	0.203 0.184	After 43 ml. paraldehyde
		4:35 P.M.	14	126.4	147.3	8.6	140.3	2.0	After 63 ml. paraldehyde
3	5-31-56	7:15 P.M.	22.2	118.3	143	6.0	0.2	2.2	Control
	6-1-56	12 N	15	116.5	147	5.3	7.52	91.9	1.1	11.955 12.345	0.233 0.237	After 27 ml. paraldehyde
		3 P.M.	16.6	101.1	127.3	5.1	119.6	2.2	4.379 3.377	0.119 0.128	After 35 ml. paraldehyde

diffuse moist rales were heard in the lungs. Pulmonary edema was thought to be present in dogs 2 and 3. All animals died of respiratory center depression in deep coma.

COMMENTS

Paraldehyde is unstable and deteriorates into several toxic substances, of which at present acetic acid and acetaldehyde are known. Chronic intoxication of rats with acetic acid causes diminished appetite, retarded growth and death in nine weeks [55]. Acetaldehyde causes mucosal damage, delirium, pulmonary edema and degeneration in the heart and liver [56]. Of the other possible decomposition products, chloracetic acid, other members of the paraldehyde series and acetals have been shown to be highly toxic [57-59].

The two cases of paraldehyde poisoning herein

described showed acidosis and bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria and leukocytosis. These effects cannot be ascribed entirely to the central nervous system action of paraldehyde. Deteriorated paraldehyde given to dogs produced acidosis and other toxic symptoms besides narcosis.

The explanation of the acidosis that was noted in the dogs and in the human subjects is by no means clear. It is probable that several factors contributed to this change. Some of the more likely are as follows:

1. A disturbance in intermediary metabolism secondary to abnormal nutrition. (a) Starvation, with resultant accumulation of ketones, depletion of glycogen and resultant lack of metabolism of carbohydrate substances to furnish the energy required for fat synthesis, the Krebs cycle, etc. (b) Overloading a carbohy-

drate-depleted system with fuels (alcohol and paraldehyde) which are mainly metabolized as two carbon fragments.

2. A disturbance in intermediary metabolism secondary to toxic effects of paraldehyde or its decomposition products upon specific enzyme systems. The shift of the lactate-pyruvate system in favor of lactate noted in dog 1 suggests impairment of intracellular oxidation with pyruvate acting as a hydrogen acceptor. The fact that dog 1 had a pH of 7.62 at the time that lactate was 8.2 mEq./L. of blood water, and a pH of 7.18 with a lactate of 7.1 is evidence that lactate alone does not explain the marked acidosis.

3. Secondary disturbances which are common to oliguria and anuria. (a) Phosphate and sulfate retention. (b) Retention of organic acids.

Any or all of the postulated mechanisms could have played a part in the two cases reported here. Both patients were chronic addicts on a poor diet. They both consumed large doses of paraldehyde which may have been deteriorated; both showed evidence of oliguria with mild azotemia. Further studies are required before one can pinpoint the mechanism involved.

Acknowledgments: The advice and assistance of Mr. Frank Stratton, Dr. William Huckabee, Dr. Joseph Dingman and Dr. Murray Blair in the preparation of this paper is gratefully acknowledged.

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Renal Tubular Acidosis with Organic Aciduria during Paraldehyde Ingestion*

Six Year Study of an Unusual Case

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THE syndrome of renal tubular acidosis was first described by Butler, Wilson and Farber [7] in 1936 and was established as the primary derangement in certain types of osteomalacia by Albright and his associates [2] in 1946. Since then a large series of investigators have studied this disturbance in renal tubular acidification mechanisms and its relationship to other specific tubular defects, such as the failure to reabsorb glucose or amino acids (as in the Fanconi syndrome). This literature, which has been reviewed in brief elsewhere [3], indicates that multiple specific tubular defects, whether acquired or inherited, may occur in various combinations and can lead to a wide variety of clinical pictures [4].

As a contribution to the understanding of the clinical diversity of these syndromes we present here the metabolic study of a case of renal tubular dysfunction which is unusual in respect to (1) the initial severity of the acidosis, (2) an episode of organic aciduria of an extreme degree related to the ingestion of paraldehyde, and (3) the ameliorated course of this patient's disease over a period of six years of detailed observation. To the best of our knowledge, metabolic acidosis as the result of the defective metabolism of paraldehyde or excretion of its metabolites has not hitherto been reported.

EXPERIMENTAL METHODS

Over the six years of the study the patient was seen as an out-patient and as an in-patient many times in the Hospital of the University of Pennsylvania. During some admissions observations were made on the medical ward. Exact balance studies, using methods previously described [5], were conducted in the Metabolic Unit of the hospital. Tests of specific renal functions were conducted by standard methods. The studies of organic acids in urine were performed by Dr. David Seligson using methods to be reported by him. §

CASE STUDY

In February 1950, A. T., a thirty-seven year old white housewife of Italian descent, was admitted to the medical ward of the Hospital of the University of Pennsylvania in an unconscious state and hyperventilating. Since it was known that the patient was

§ Unpublished method. The method is based on the measurement of acids after barium-insoluble anions (phosphate, sulfate and some citrate) are removed and after chloride is accounted for. All cations including most of the amino acids were removed on an ion-exchange resin in the hydrogen cycle. Organic acids were measured by titrating to pH 7.4. Under the conditions of this method organic acids which are in their ionic form in body fluids are measured, and artifacts resulting from conversion of weak acids to anions at pH values above 7.4 are avoided. Non-volatile organic acids are those which remain after drying in a warm air draft (40 to 70°C.). Volatile acids are calculated by difference.

* From the Chemical Section and the Renal Section of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. This case was first presented to the Interurban Clinical Club in April 1952 and was reported by title to the Association of American Physicians, May 1 and 2, 1956. Aided by grants from the National Heart Institute of the United States Public Health Service (H-340 and H-405) and by the C. Mahlon Kline Fund of the Department of Medicine, University of Pennsylvania School of Medicine.

† Established Investigator of the American Heart Association.

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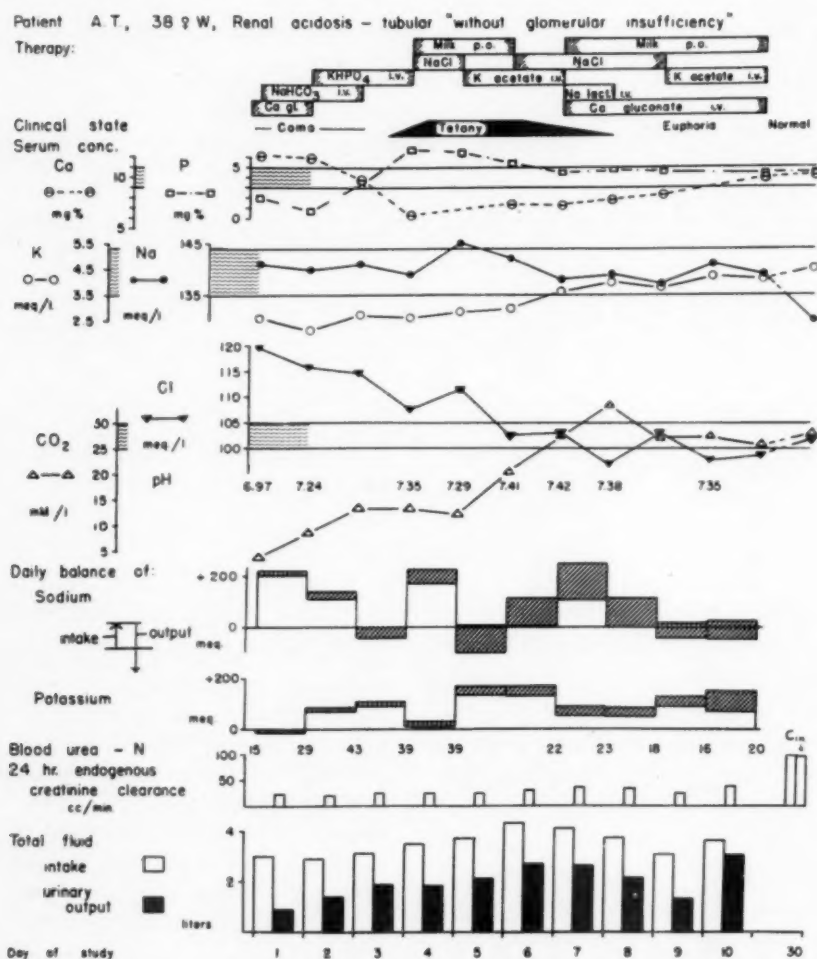


FIG. 1. Patient A. T. Serum levels and balances of electrolytes during treatment of initial episode of severe acidosis (February to March 1950). Normal ranges of serum values are enclosed between parallel lines. In the balance data, clear spaces above the zero line show positive balances (or retention), shaded areas below the zero line, negative balances (losses).

TABLE I
PATIENT A. T.: STUDIES OF SPECIFIC RENAL FUNCTIONS*

	Normal Values†	March 1950	October 1951‡	March 1952	February 1956
Glomerular filtration rate (inulin clearance) ml./min./1.73 sq. m.	109 ± 14	89	108	127	111
Effective renal plasma flow (PAH clearance) ml./min./1.73 sq. m.	592 ± 153	445	557	548	645
Extraction PAH per cent	91 ± 5	81	...	91	...
Tm _{PAH} mg./min./1.73 sq. m.	77 ± 11	55	98	80 98§	78

* Average of three clearance periods.

† From H. W. Smith [16]; means and standard deviations.

‡ During prolonged ingestion of paraldehyde.

§ During sodium acetate infusion.

under psychiatric care the first impression was that her clinical picture was hysterical in origin. However, the persistence of the clinical condition, the absence of tetany, and the laboratory findings of a total carbon dioxide content of venous serum of 4 mM./L. and a pH of arterial blood of 6.97, as well as a serum chloride concentration of 120 mEq./L., showed that the patient was in severe hyperchloremic metabolic acidosis. Additional laboratory findings on admission were as follows: sodium 136 mEq./L.; potassium, 2.6 mEq./L.; calcium 12.0 mg. per cent; phosphorus, 1.9 mg. per cent; blood urea nitrogen, 15 mg. per cent; sugar, 85 mg. per cent.

In the absence of azotemia, hyperglycemia or ketonuria, a diagnosis of renal tubular acidosis was made. The patient showed no x-ray evidence of osteomalacia or of nephrocalcinosis. The acidosis and the associated depletion of water and electrolytes were successfully treated with intravenous solutions of sodium, potassium and calcium salts, as shown in Figure 1. It is worthy of note that the infusion of

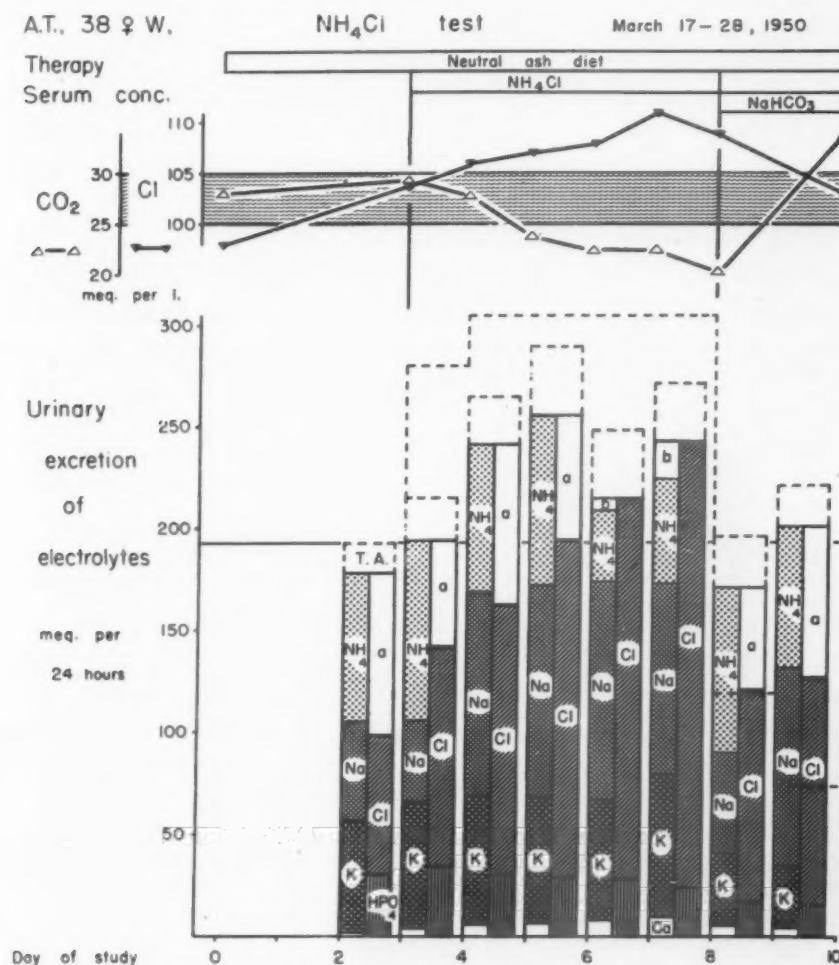


FIG. 2. Patient A. T. Urinary response to ammonium chloride test (March 1950). The renal tubular response was inadequate in that the excretion of ammonium ion was not increased in response to the excess chloride load; "fixed" cations, Na^+ , K^+ and Ca^{++} were lost instead. The patient became acidotic. The dotted line rising above and enclosing all of the urine ionic columns represents the intake of ammonium chloride during the test period. Titratable acidity is represented by T. A., undetermined anion by a, undetermined cation by b.

potassium phosphate solution (chloride being contraindicated) led to a rapid fall in serum calcium concentration which, in conjunction with a slowly rising level of extracellular potassium and a rising arterial pH, induced a state of profound tetany. (Fig. 1.) This was successfully combatted by changing to the infusion of potassium acetate solution and by the liberal use of calcium gluconate.

One month after this admission, when Patient A. T. was no longer acidotic, studies were made of her renal function. (Table 1.) Depression of tubular function was indicated by low values for maximal tubular transport of para-aminohippurate (TmPAH) and for extraction of PAH from the blood passing through the kidney (EPAH). Renal blood flow and glomerular filtration rate (inulin) were within the normal range, although the twenty-four-hour creatinine clearance during the previous admission had at that time suggested depression of glomerular filtration rate. (Fig. 1.) Ammonium chloride was then administered for

five days, according to the technic of Albright et al. [6], to ascertain whether or not she had a defect in the tubular defense against metabolic acidosis. Such a defect was clearly demonstrated as, at the end of five days, the patient was again moderately acidotic and hyperchloremic and the ammonium ion content of the urine had not increased. (Fig. 2.) This was in marked contrast to the effect of a comparable dose of ammonium chloride on control subjects [6]. The patient was discharged on alkali therapy (sodium citrate), as recommended by Albright.

During the next year and a half the patient was admitted a number of times in varying degrees of acidosis associated with vomiting, psychic disturbances and occasionally, convulsions (possibly related to the withdrawal of barbiturates to which she was habituated). (Fig. 3.) However, the diagnosis of epilepsy was considered likely and the patient was given dilantin,[®] which she has received ever since. In March 1951 her psychiatrist administered paraldehyde

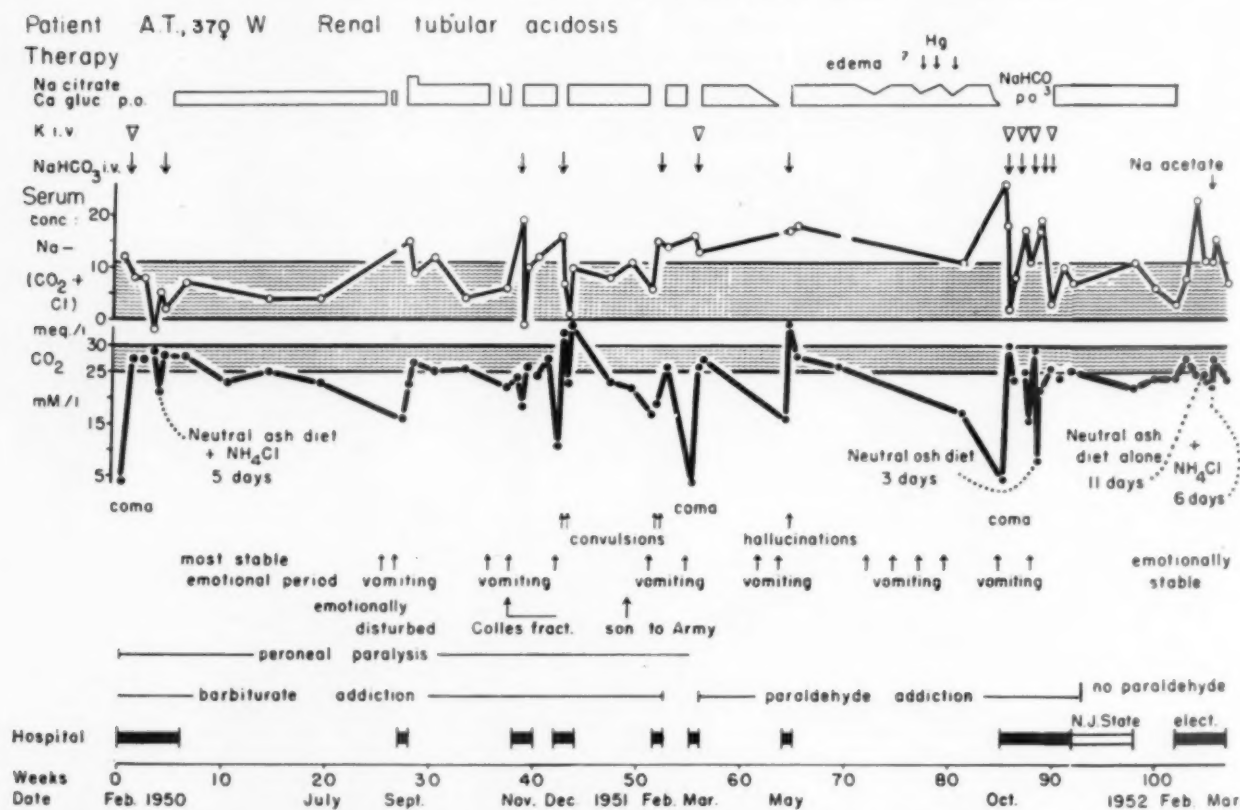


FIG. 3. Patient A. T. Course during the first two years. The serum levels of undetermined anion and of total carbon dioxide are shown in conjunction with the principal clinical events. Values for undetermined anion are derived and represented by $\text{Na} - (\text{CO}_2 + \text{Cl})$.

hyde to wean her from barbiturates, and she then became habituated to paraldehyde.

In October 1951 the patient was readmitted in severe acidosis, but this time her serum chloride was low rather than high, and she had a very high undetermined anion concentration in her serum. (Fig. 3.) Following treatment for the acidosis with alkali, she was given a neutral ash diet to determine again her ability to acidify her urine. Amazingly at the end of the third day of the control period on a neutral ash diet the patient's serum carbon dioxide content had dropped to 8 mM./L. and the patient exhibited a massive organic aciduria. (Fig. 4.) Study of these organic acids revealed that about half were volatile organic acids (much of which was presumed to be acetic acid). (Table II.) The organic acids have not been identified although a great many have been ruled out. During this period the patient was receiving massive doses of paraldehyde, 60 to 120 cc. daily (1,300 to 2,600 mEq. of potential acetate anion). Since it was impossible to control the patient, she was sent to a state hospital for care and treatment of her drug habituation. The prognosis at that time appeared to be very poor.

In January 1952 the patient was discharged from the state hospital, cured of her addiction to paraldehyde, and since then her health has steadily improved.

In February 1952 she was readmitted electively to the Hospital of the University of Pennsylvania for study of her renal tubular function. At that time she had no excess organic acids in her urine and her ability to meet an acid stress of ammonium chloride, if not quite normal, was improved over that shown by the previous test. (Fig. 5.) Acute renal clearance studies were again carried out and the patient's glomerular filtration rate and effective renal plasma flow were found to be within the normal range, as were the TmPAH and the extraction of PAH. In addition, the patient was given a sodium acetate infusion and it was shown that the acetate raised the TmPAH to a high level, coinciding with levels observed in October 1951 when she was taking paraldehyde. This observation suggests the speculation that endogenously formed acetate may have raised the TmPAH observed in October 1951. In any event the studies indicated that the patient's tubular function had greatly improved. (See Table I.)

In November 1952 the patient was electively readmitted to ascertain whether or not she had a defect in the ability to oxidize acetate, the thought being that the prior heavy paraldehyde medication may have brought out such a metabolic abnormality. Accordingly the patient was given a neutral ash diet, and then fed successively larger amounts of am-

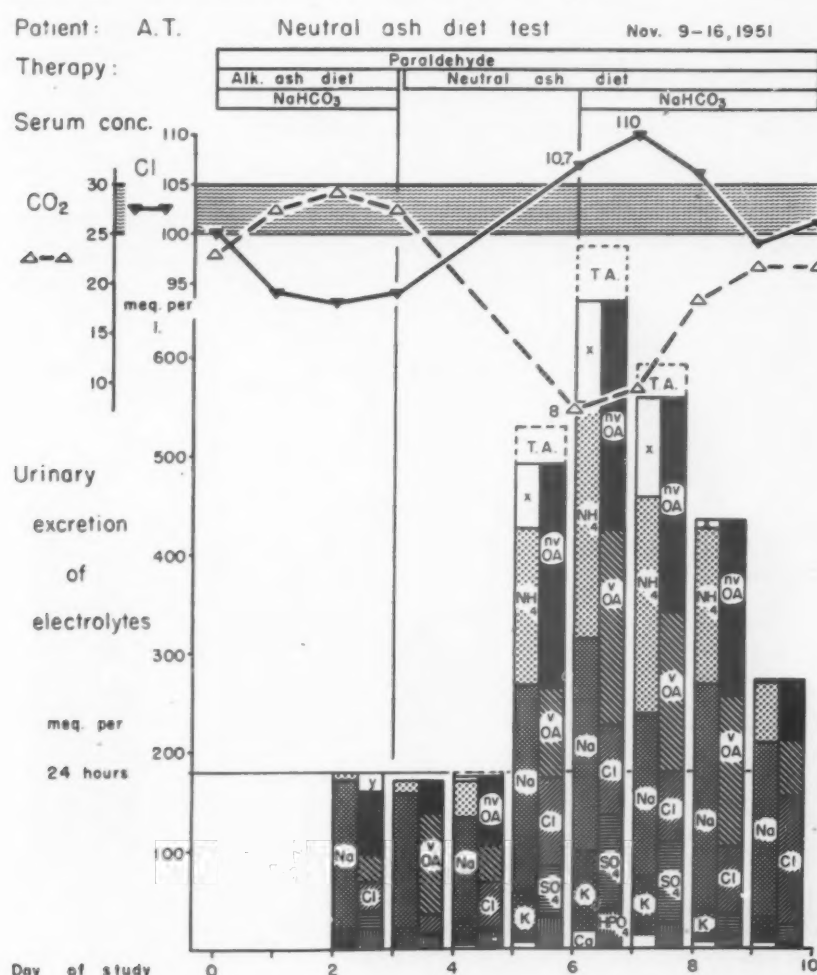


FIG. 4. Patient A. T. Severe organic aciduria and metabolic acidosis developing on a neutral ash diet and paraldehyde (November 1951). nvOA represents non-volatile organic acids, vOA volatile organic acids, x undetermined cation, and y undetermined anion.

monium acetate over five days, reaching on the fifth day a total dose of 50 gm. or 650 mM. of this substance. There was no significant increase in the organic acids in the urine. (Fig. 6.) This appeared to rule out an innate defect specifically in relation to acetate oxidation.

During the subsequent three years the patient has been much improved in health. She has twice been admitted for mild relapse into medication difficulties. In July 1953 she came in somewhat confused and with an elevated barbiturate level in her spinal fluid, but she was not acidotic. In April 1954 she was admitted in a drowsy state, again not severely acidotic but with a high bromide level in her spinal fluid. Except for these two relapses the patient apparently has not taken any drugs. During this time the patient has many times exhibited slight depression of her total carbon dioxide content in venous serum, and at times this low carbon dioxide level was associated with an alkaline urine. During the years 1950 to 1952 the mean of all serum carbon dioxide levels was 18.1 ± 8.2 (1 standard deviation), from 1952 to 1954, $24.0 \pm$

2.0 and from 1954 to 1956, 25.2 ± 2.7 . (Fig. 7.) Hence the metabolic acidosis regressed and has continued to

TABLE II
PATIENT A. T.: ORGANIC ACIDS IN URINE DURING
PARALDEHYDE INGESTION AND NEUTRAL ASH
DIET (NOVEMBER 1951)

Day of Study	Total Organic Acids (mEq./24 hr.)	Non-volatile* (mEq./24 hr.)	Volatile* (mEq./24 hr.)	Urine Volume (ml.)
2	92	64	28	1,940
3	136	32	104	3,840
4	110	73	37	1,200
5	322	230	92	2,185
6	435	235	200	4,115
7	380	216	164	2,700

* For definitions of non-volatile and volatile organic acids, see footnote § on page 977.

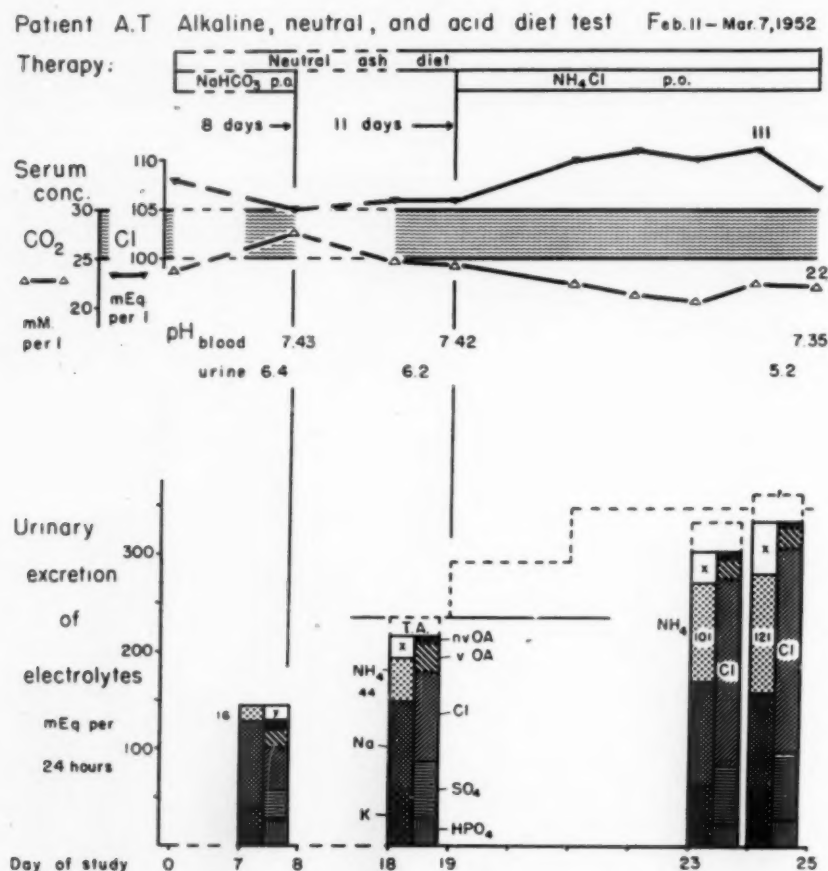


FIG. 5. Patient A. T. Urinary response to ammonium chloride test (February to March 1952). The renal compensation for metabolic acidosis was more adequate than in 1950 but did not prevent a mild hyperchloremic acidosis. Total organic acid output in the urine was normal throughout, even on day 19 when the patient underwent severe psychic stress.

regress without continuation of alkalinization therapy. Sometimes the serum chloride was high, sometimes not, and the undetermined anions were occasionally high. In June 1955 the arterial blood of the patient was checked to determine whether or not a mild chronic respiratory alkalosis might be responsible for the low total carbon dioxide and the alkaline urine. The pH was low normal and the indications were that the patient was suffering from a very mild metabolic acidosis.

In February, 1956, six years after the initial admission, the patient was electively admitted and again was given ammonium chloride while taking a neutral ash diet. Moderate impairment of the renal compensation for metabolic acidosis again was demonstrated, although the standard renal hemodynamic measurements and the tubular maximal transport of PAH were still within the normal range. (Table 1.) The renal acidification defect was not due to absence of the carbonic anhydrase system in the tubules since the patient responded to intravenous infusion of a carbonic anhydrase inhibitor by excreting an alkaline urine with large amounts of bicarbonate. No abnormal amounts of organic acid were currently demonstrated in her urine.

COMMENTS

Renal tubular acidosis is now well recognized to be associated with a wide variety of specific defects of renal tubular function. Such defects may include defective tubular reabsorption of water, glucose, phosphate, calcium, amino acids, organic acids and bicarbonate. Jackson and Linder [4] have classified the syndromes produced into unifactorial and multifactorial conditions, the former involving but one of these tubular transport systems, the latter involving more than one. The classic Fanconi syndrome includes defective tubular reabsorption of glucose, phosphate and amino acids [7] whereas the typical case of renal tubular acidosis exhibits multiple manifestations of defective tubular reabsorptive functions in respect to phosphate, bicarbonate and, on occasion, organic acids [8]. Recent evidence [9] indicates that these specific defects may overlap and that the patient diagnosed as having the Fanconi syndrome because of glycosuria and aminoaciduria may also have a

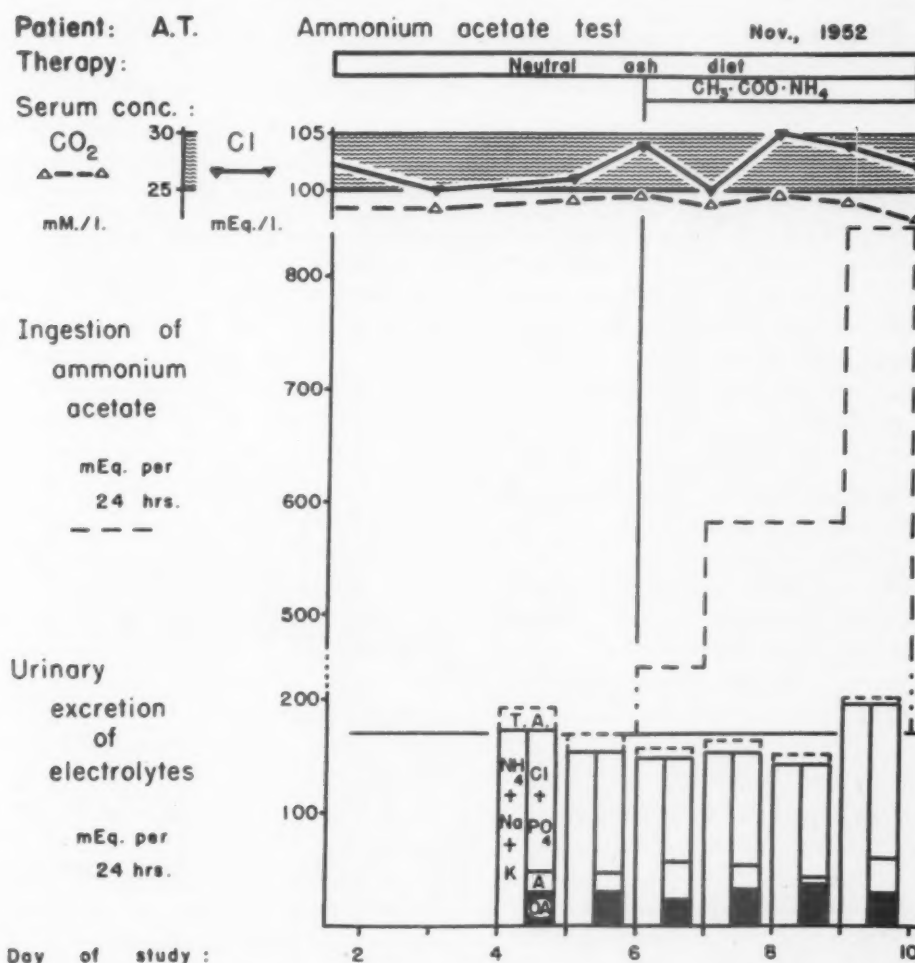


FIG. 6. Patient A. T. Response to ingested ammonium acetate. The ingested dose of these metabolizable anions and cations reached a level of 650 mEq. on the fourth day, yet no increase in urinary organic acids or systemic acidosis appeared. The patient evidently could metabolize acetate at this time.

hyperchloremic metabolic acidosis due to defective tubular excretion of hydrogen and reabsorption of bicarbonate. Moreover, the pattern of individual tubular defects may vary in magnitude from time to time in the same patient. This is illustrated by Patient A. T. reported here, who originally showed a hyperchloremic metabolic acidosis in 1950 but one and one-half years later, when again in acidosis, had a lowered chloride level and a high serum concentration of undetermined anions.

Considerable variation also occurs in the renal cation wastage which is secondary to the impaired tubular acidification. Resultant depletion of calcium classically leads to osteomalacia, but a large portion of these patients (including Patient A. T.) showed no overt osteomalacia by x-ray. Potassium depletion, with hypokalemia, and sodium depletion are both common sequelae and may be present to a variable degree from

patient to patient or in the same patient. Much remains to be learned of the factors which govern the relative losses of these several cations in this disease state.

The observations on renal function as measured by conventional methods require some comment. Other workers have observed little change in glomerular filtration rate and effective renal plasma flow [10]. Aside from the usual response to acid loads, depression of tubular function was shown most clearly in our patient by depression of TmPAH and EPAH . The high TmPAH observed in the study performed during the paraldehyde habituation should be noted. Mudge and Taggart have suggested that acetate may act as one of the important rate-limiting factors in PAH tubular transport, and they have shown that infusions of acetate are capable of increasing TmPAH [17]. Our patient was given a sodium acetate infusion, and a distinct rise in

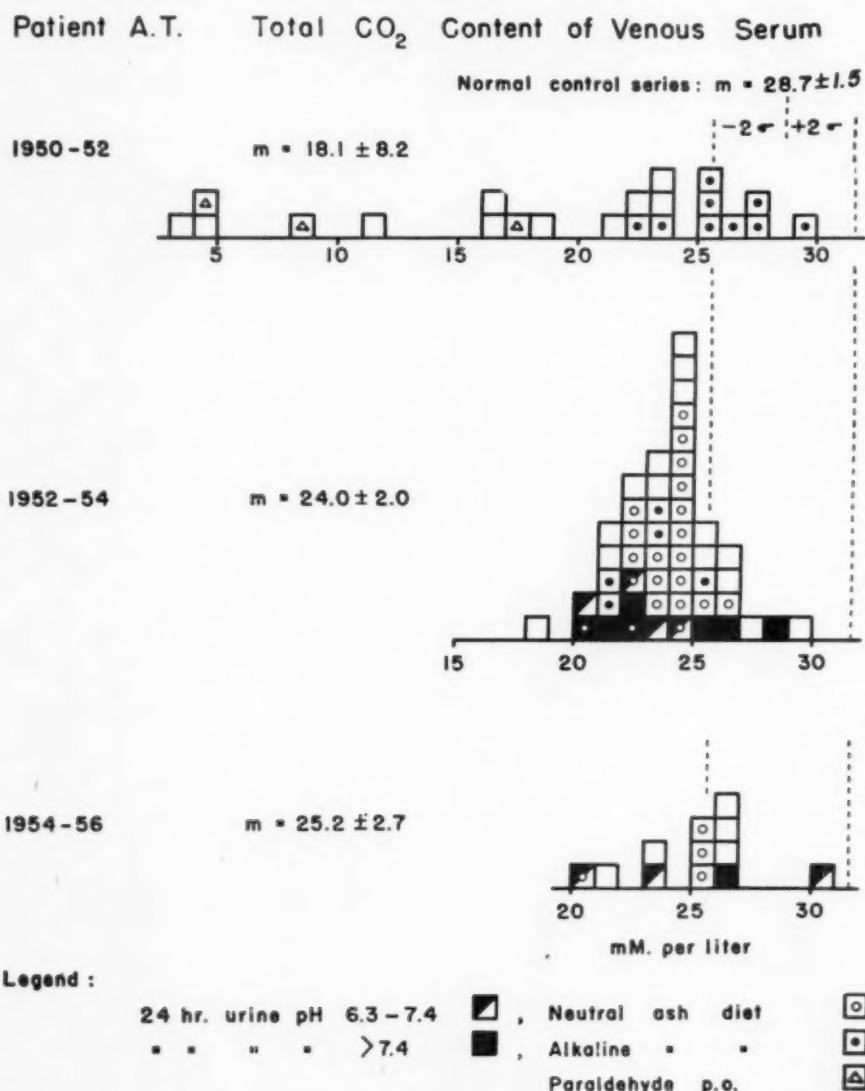


FIG. 7. Patient A. T. The distribution of venous serum levels of total CO₂ in two year periods, over the last six years. The patient continues to show a mild depression of the serum CO₂ content with corresponding abnormal amounts of bicarbonate in the urine.

Tm_{PAH} was noted. The fact that the Tm_{PAH} measured previously, during the period of paraldehyde ingestion, corresponded to the high value reached during the acetate infusion in the later study (Table 1) suggests the interesting possibility that the high volatile organic acid fraction (suggesting acetate derived from paraldehyde) may have enhanced the Tm_{PAH}. All these categories of renal function have returned to normal levels coincidentally with the patient's improvement in ability to acidify her urine and in her general health.

The organic aciduria exhibited by our patient in November 1951 constitutes the most remarkable feature of her case. Amino acids have been the principal organic acids found in pa-

tients with renal tubular acidosis or the Fanconi syndrome; these have been studied extensively by a series of investigators, including McCune *et al.* [8], Dent [12], and Milne, Stanbury and Thomson [9]. Other organic acids have seldom been reported and then only in small amounts; McCune *et al.* [8] found only 11 per cent of non-amino organic acids in their patient with the Fanconi syndrome. In our patient the twenty-four-hour output of total organic acid reached a peak (Fig. 4, Day 6) of 435 mEq., of which 200 mEq. were volatile organic acids much of which was presumed to be acetic acid. The non-volatile fraction of these organic acids, 235 mEq., has not been identified. Chromatography by the method of Busch *et al.* [13] indicated that 90 per cent of

this fraction was not citric, β -hydroxybutyric, succinic, lactic, fumaric or malic acid. Acetylated amino acids are a possibility but the answer is not known. In any case, the total quantity of organic acids excreted was tremendous and, in retrospect, must be related to the metabolism of the large amount of paraldehyde consumed (1,300 to 2,600 mEq. of potential acetate) or represents the products of metabolic pathways deranged in some way by a toxic effect of the paraldehyde itself.

Metabolic acidosis due to paraldehyde ingestion, to the best of our knowledge, has not been reported prior to this case report and the accompanying reports of Hayward and Boshell and of Waterhouse [14].* Paraldehyde toxicity, often with a fatal result, has been reported not infrequently [15]. But the pharmacologic effect has been one of circulatory collapse and respiratory depression, no evidence of a metabolic acidosis being reported.

Normally, paraldehyde is oxidized almost completely to carbon dioxide and water; only about 10 to 30 per cent is excreted unchanged via the lungs, and practically none appears in the urine [15]. The first step in oxidation is presumably splitting of paraldehyde to acetaldehyde. In the course of normal metabolism, acetaldehyde is oxidized by dehydrogenation in the presence of aldehyde dehydrogenase to acetate. The latter is converted to acetyl coenzyme A which can enter the tricarboxylic acid cycle where it is oxidized to carbon dioxide and water. The latter step can occur in all the tissues. The appearance of a large amount of volatile organic acids (which we presume to be mainly acetic acid) in the urine suggests that acetaldehyde oxidation was adequate but that a temporary failure of acetyl coenzyme A synthesis had occurred or that the acetyl coenzyme A synthesizing mechanism had been saturated, which led to the accumulation of acetate in body water and hence to excretion by the kidney. If acetyl coenzyme A had formed in the liver but had not entered the

tricarboxylic acid cycle, condensation with itself to form acetoacetic acid would have been expected, with the excretion of large amounts of acetone bodies. Ketonuria was not observed.

This hypothesis of a possible derangement of acetate metabolism in this patient has been offered, but an explanation of the cause is lacking as is an explanation for the other organic acids appearing in the urine. The fact that the magnitude of the organic aciduria as shown in Figure 4 was roughly proportional to the fall in serum carbon dioxide level and rise in serum chloride level suggests that the impairment of organic acid metabolism may have been influenced by acidosis itself, presumably of tubular origin. Additional evidence in favor of this view lies in the patient's subsequent ability to oxidize a large acute load of acetate when she was not acidotic. But renal tubular acidosis itself cannot be the sole factor because massive organic aciduria was not detected prior to paraldehyde ingestion when the patient was severely acidotic. The other possibility is that the ingestion of paraldehyde for many months preceding may have exhausted or saturated systems for organic acid oxidation, including acetyl coenzyme A, or may have impaired these systems by some undefined toxic effect.

The problem of the organic aciduria has not been definitively resolved in this patient but we have not felt morally justified in placing this patient on paraldehyde again for study purposes in view of her freedom from drug habituation since the episode reported in this paper. In conclusion, the patient's clinical course appears to have been determined by two entities, renal tubular acidosis and a derangement of organic acid metabolism probably attributable to the ingestion of paraldehyde, the only apparent relation between the two being a possible effect of acidosis on the magnitude of the organic acid disturbance.

SUMMARY

Studies over a six year period are reported of a middle-aged white woman who was originally admitted in extreme metabolic acidosis due to a renal tubular defect in acidification and conservation of bicarbonate and cation. The patient has improved greatly over the years of observation although the tubular defect persists to a mild degree.

At the end of a long period of habituation to the ingestion of large amounts of paraldehyde,

* One other case, possibly of this type, has been observed and kindly reported to us by Dr. Martin Epstein of the New Jersey State Hospital, Trenton. The patient, a chronic alcoholic receiving paraldehyde, died at the end of a four-day period of hyperventilation and oliguria with a blood urea nitrogen of 50 mg. per cent and a total serum carbon dioxide of 8 mM./L. Organic acids in the urine were not measured, and the role of the renal failure in the acidosis was not defined; six days before the acidosis was discovered, however, the blood urea nitrogen was low normal (9 mg. per cent).

the patient exhibited an extreme degree of organic aciduria associated with a systemic acidosis while on a neutral ash diet, a phenomenon not subsequently induced when comparable amounts of ammonium acetate were administered. It is postulated that the organic aciduria may have arisen in part from an overburden of paraldehyde-derived acetate on the system for acetate oxidation, or from an impairment of organic acid oxidation by paraldehyde or by acidosis, or from any combination of these effects.

Acknowledgments: We gratefully acknowledge the kind cooperation of Dr. John Reinhold, Chemical Division, William Pepper Laboratory, Hospital of the University of Pennsylvania, in the performance of the clinical chemical determinations. We gratefully acknowledge the assistance of Drs. H. G. Barker, A. P. Crosley, Jr., and A. Cummins in the specific renal function studies.

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Metabolic Acidosis Occurring during Administration of Paraldehyde*

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IT is rare to encounter patients with severe metabolic acidosis in whom the etiology of the acidosis cannot be readily established. The common causes, such as diabetes, renal disease and loss of pancreatic juices, are all easily diagnosed by simple clinical or laboratory data. The more uncommon causes such as hepatic failure and ingestion of methyl alcohol or organic acids (boric and salicylic acids) also do not pose serious diagnostic problems. We are reporting a case of metabolic acidosis in which none of the above factors played a significant role, and in which we now believe the etiology to have been paraldehyde intoxication.

CASE REPORT

A forty-eight year old white housewife was admitted to Strong Memorial Hospital on November 27, 1955 with chief complaints of nausea, vomiting and increasing weakness of three days' duration. Since 1953 the patient had been under psychiatric care relative to a psychotic depressive reaction precipitated by the death from a brain tumor of a domineering sister, the emotional disturbance of her daughter, and the recent failure of a corneal transplant operation. She had had frequent migraine headaches and occasional convulsive episodes. Extensive study had failed to reveal evidence of organic brain disease. She had had several admissions to the psychiatric service where improvement had occurred with supportive therapy, and during one admission she received nine electroconvulsive treatments. Because of anxiety and insomnia she had been taking paraldehyde, 8 cc. each night and 4 cc. every four hours during the day as necessary. This dose had been gradually increased so that prior to admission she had been taking up to 80 cc. of paraldehyde per day. In addition she had been taking meprobamate and chlorpromazine up to 200 mg. a day. For several months, nausea and vomiting had occurred intermittently but had become persistent for the three days prior to admission.

Physical examination showed the patient to be a

well developed, thin white woman who appeared fearful but well oriented and lucid. Temperature was 37.5°C.; pulse, 80; respirations, 30; and blood pressure 120/80 mm. Hg. Respirations were rapid and deep. The odor of paraldehyde was on her breath. Signs of dehydration were present. There was no icterus or cyanosis. Other than the bilateral keratoconus the remainder of the physical examination was within normal limits.

Laboratory examination revealed the hematocrit to be 51 per cent and the white blood cell count, 37,200 per cu. mm. The specific gravity of the urine was 1.030, the pH 6.0. There was a 1 plus albumin in the urine but no sugar, acetone or abnormal cells.

The events of the first hospital day are recorded in some detail. The patient was given 10 cc. of paraldehyde by rectum and 25 mg. of chlorpromazine intramuscularly at 7 P.M. on November 27, 1955. She received another dose of chlorpromazine at 1 A.M. on November 28, 1955 and another 10 cc. of paraldehyde at 2:30 A.M. A house officer was called shortly after this because of a drop in the patient's blood pressure and other signs of shock. The patient was responsive at that time, and hyperventilating; she told of numbness and tingling of her extremities. An infusion of levophed® in isotonic saline solution was started, with transient improvement in the blood pressure. Because of the negative urine findings, the idea was briefly entertained that the hyperventilation was on an hysterical basis and rebreathing was instituted without effect. At the patient's request 12 cc. of paraldehyde was given per os for sedation at 4:30 A.M. The patient remained hypotensive despite the levophed. At 7:00 A.M. the blood carbon dioxide content was found to be 2 mm./L. and a venous pH of 7.03 confirmed the diagnosis of severe metabolic acidosis. At this time alkali therapy was started. Subsequent fluid administration and determinations of the plasma electrolytes are summarized in Table 1. Following the administration of fluid and alkali the blood pressure returned to its initial value of 120/80 mm. Hg and was stable. The following day the urine was noted to be grossly bloody. Oliguria was present for the next six days and the patient followed a classic course of partial

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TABLE I
SERUM ELECTROLYTE CHANGES AND TREATMENT DURING RECOVERY FROM PARALDEHYDE
INTOXICATION

Date	Time	Serum					Treatment
		Carbon Dioxide (mM/L.)	pH	Chloride (mEq./L.)	Sodium (mEq./L.)	Urea Nitrogen (mg. %)	
11/28/55	7 A.M.	2	7.03	118	138	25	1,000 cc. 1/6 M sodium lactate
	11 A.M.	7	7.06	7.5 gm. sodium bicarbonate
	3 P.M.	5	115	15 gm. sodium bicarbonate 1,000 cc. 1/6 M sodium lactate
11/29/55	8 P.M.	20	103	144
	8 A.M.	23	105	143	52
12/15/55	28	109	147	7

renal shutdown. The blood urea nitrogen reached a peak value of 124 mg. per cent four days after diuresis had started. This was the only complication of her severe metabolic acidosis. She was discharged from the hospital on December 22, 1955. The urine then was normal and blood urea nitrogen was 12 mg. per cent.

Following discharge from the hospital the patient was followed up by her family physician, and at weekly intervals by a psychiatrist. She was maintained on a regimen of dilantin sodium and was given moderate doses of paraldehyde to help her to sleep. She got along quite well until May, 1956 when her son became involved with the police in a charge of theft. Thereafter she became increasingly depressed and agitated and had frequent episodes of gastric pain, nausea and vomiting. These symptoms were unrelieved by chlorpromazine. It had been thought that the patient was taking a maximum of 20 cc. of paraldehyde a day under the strict supervision of her husband. It was later determined that she had secretly gained access to the key to the medicine cabinet and had been ingesting undetermined but larger amounts than had been prescribed. Her symptoms became more severe and after four days of persistent nausea and vomiting she was again admitted to Strong Memorial Hospital on July 11, 1956.

At the time of admission the patient was somewhat confused. Temperature was 38°C.; pulse, 128; and blood pressure, 115/90 mm. Hg. Respirations were 20 and deep. The breath smelled strongly of paraldehyde. There was evidence of dehydration. The remainder of the physical and neurologic examinations were unchanged.

Laboratory findings were as follows: hemoglobin, 17 gm. per cent; hematocrit, 50 per cent; white blood count, 8,000 cells per cu. mm. Blood chemistry deter-

minations: blood carbon dioxide, 10 mM/L.; chlorides, 121; sodium, 144; potassium, 3.85 mEq./L. The blood urea nitrogen was 7 mg. per cent.

The patient was given 2,000 cc. of 1/6 molar sodium lactate and 1,000 cc. of normal saline solution intravenously. The following morning the plasma carbon dioxide was 20 mM/L.; chlorides, 112; sodium 145; and potassium, 3.4 mEq./L. The blood urea nitrogen was 7 mg. per cent; fasting blood sugar, 88 mg. per cent. Subsequently the patient was able to take fluids adequately by mouth and the urinary output varied from 1,300 to 1,800 cc. per day. Subsequent determinations of plasma electrolytes were normal. On the second hospital day the patient became increasingly confused and hallucinated. She was transferred to the psychiatric ward where over the course of the subsequent week her mental confusion and hallucinations cleared and she was discharged from the hospital on July 21.

Since that time she has received no paraldehyde and her only other admission to the hospital was an elective one in January, 1957 for the study of renal function. The urine examination was normal and the urea clearance was 61 per cent of normal. Ammonium chloride, 8 gm. daily, was given for two days, without significant change in her serum electrolytes. The urinary pH on the first day of ammonium chloride administration was 5.0 and the titratable acidity was 15 mEq. During the second twenty-four hours the urinary pH was 4.5 and the titratable acidity was 30 mEq.

COMMENTS

There is little question that this patient had a profound metabolic acidosis on her first admission. The etiology of this was of considerable concern. The common causes were promptly

ruled out by laboratory procedures. It was believed at the time the acidosis was recognized that this must be due to some toxic agent, and for this reason the urine was tested for methyl alcohol, with negative results. Repeated questioning of the patient after recovery convinced us that she had taken no other substances than those prescribed for her. The final opinion on discharge from the hospital the first time was metabolic acidosis secondary to some exogenous agent, probably paraldehyde. The recurrence of mild acidosis some six months later, again after the ingestion of rather large amounts of paraldehyde, is added incriminating evidence against this substance.

The metabolism of paraldehyde in the human body is not well understood. It is known that most of this substance is metabolized, probably by the liver [1], but the intermediate degradation productions are not known. It seems quite likely that this patient was unable to excrete or to metabolize completely the administered paraldehyde rapidly enough to prevent the accumulation of some unidentified acid degradation substances in her blood. Unfortunately we have no studies of the urinary secretion of organic acids in this patient. The serum electrolyte data obtained on the first admission support the conclusion that there was an unidentified anion in her serum. One gains the impression that there was rather poor renal compensation for the degree of acidosis present; however, the data and course make it unlikely that the acidosis itself was produced by failure of the renal tubular acidifying mechanisms.

Although toxic doses of paraldehyde result

in respiratory failure, one of the notable effects of paraldehyde sedation is lack of respiratory depression. In certain cases of reported toxicity the phenomenon of hyperventilation is stressed. In one report diabetic acidosis was considered as the etiology of the hyperventilation as it was in this case [2]. In another case report, the plasma carbon dioxide was reported as 15 mM/L. forty-two hours after the administration of the drug [3]. The labored respirations of paraldehyde toxicity have usually been believed to be due to the untoward effect of the pulmonary capillaries. Possibly, in certain cases a metabolic acidosis is the causative factor.

SUMMARY

A case report is presented of a patient in whom metabolic acidosis developed during paraldehyde ingestion. The study of this patient sheds no light on the mechanism but this complication of excessive paraldehyde intake is worthy of more clinical attention.

Acknowledgment: The authors wish to thank Dr. Roger S. Allison of Rochester, New York for the opportunity of seeing this patient.

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Ammonia Intoxication during Treatment of Alkalosis in a Patient with Normal Liver Function*

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AMMONIA is considered by some observers to be the toxic agent in the production of the neurologic complications of liver disease [1-5]. Direct evidence that the administration of ammonium salts in the absence of hepatic disease can produce the same neurological signs and symptoms would be helpful in further demonstrating that ammonia is important in the central nervous system manifestations of hepatic coma.

In the patient herein reported the development of neurologic signs coincidentally with the intravenous administration of ammonium chloride was impressive. Signs and symptoms of central nervous system intoxication, such as are usually seen in hepatic coma, were encountered in a patient without evident liver disease. They occurred during treatment of severe alkalosis with intravenous ammonium chloride.

In animals it was demonstrated as early as 1893 that the principal effects produced by injected ammonium chloride were twitches, tremors progressing to tetany, convulsions, opisthotonus, irregular respirations, salivation, somnolence and lassitude [6]. Hahn and collaborators observed in 1893 that a dog with an Eck fistula could not tolerate a high protein diet, a characteristic syndrome known as "meat intoxication" developing after a short time [7]. These investigators, who considered the possible role of ammonia, were able to reproduce the syndrome by feeding ammonium chloride.

Sherlock and collaborators, and Davidson and collaborators have reported the appearance of the neurologic signs of hepatic coma during oral administration of ammonium chloride in

patients with known liver disease, but in their control patients without hepatic disease no neurologic changes occurred [8-10].

A patient has been observed in whom, following anastomosis of the superior mesenteric vein to the inferior vena cava, transient episodes of disorientation developed progressing to stupor [11]. This patient may have had a normally functioning liver but complete evaluation of preoperative hepatic function is not included in the report. The authors state "this neurologic disorder was transient, completely reversible and unaccompanied by any demonstrable chemical change other than intermittent precipitous elevations of the concentration of ammonia in the blood." The episodes could be precipitated by oral administration of ammonium chloride or by feeding a high protein diet.

Untoward symptoms developing coincidentally with oral ammonium chloride therapy have been reported in patients with severe cardiac and renal disease, but impaired hepatic function seems a likely complication of heart failure [12]. In fact, elevated blood ammonia levels have been demonstrated in congestive heart failure, indicating there may be some functional impairment of the liver in respect to ammonia metabolism in congestive failure [13]. In azotemia it has been observed that the ammonia concentration in gastric juices reaches levels of 70 to 100 mg. per cent, suggesting that under these conditions urease activity in the stomach releases considerable quantities of ammonia from urea [14]. This additional production of ammonia by the stomach may result in a higher

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systemic blood ammonia level or may indirectly influence the metabolism of ammonia by brain or other tissues.

Recently Eiseman and his co-workers infused various ammonium salts into a carotid artery of an unanesthetized dog without liver disease and were able to produce progressive neurological abnormalities indistinguishable from advancing hepatic coma [15]. The neurologic changes consisted of convulsive twitching of the extremities and reflex hyperactivity progressing to reflex hypoactivity and coma. These abnormalities could be provoked by infusions of ammonium chloride, ammonium citrate or buffered ammonium hydroxide and seemed to be independent of alterations in blood pH. The onset of the neurological symptoms followed a lag period of one to five hours of elevated blood ammonia.

It has been suggested previously that infusions of ammonium salts in patients with normal liver function should, if rapid enough, produce the effects of ammonium intoxication [16], but there has been no documentation of such an event. Because toxic signs coincident with ammonium chloride therapy for alkalosis did develop in the case to be reported, the sequence of events is of interest.

CASE REPORT

C. P., a sixty-one year old barber, was admitted to the Seattle Veterans Administration Hospital on February 25, 1956, with a one month history of dull epigastric burning pain, persistent vomiting and a 25 pound weight loss. There was at least a fifteen year history of peptic ulcer symptoms with abdominal operations in 1943 and 1950 for the closure of perforations. Since 1950 the patient had been taking an ulcer regimen which included a soft diet, milk and bicarbonate of soda. The symptoms were adequately controlled until two months prior to this admission when the bicarbonate of soda would no longer relieve the epigastric distress. He consumed approximately one box of bicarbonate of soda a week and up to 1 quart of milk daily. For one month before admission he had had postprandial nausea and had vomited large amounts of fluid and food in the evening. No history of renal calculi or bone symptoms was elicited.

The patient admitted drinking 1 to 2 pints of whiskey per day prior to 1940. Since that time all alcoholic intake was denied. There was no history of jaundice or hepatic disease.

The patient appeared poorly nourished, with evidence of weight loss. The respiratory rate was 20, pulse, 72 and regular; and blood pressure, 124/65 mm Hg. There was an increase in the anterior-posterior

diameter of the chest with decreased breath sounds at the bases but no rales were heard. The heart was normal in size with no murmurs. Abdominal laparotomy scars were seen. Distention of the stomach seemed apparent as there was a succussion splash in the upper part of the abdomen. The remainder of the physical examination, including the neurological examination, was normal. The patient was fully alert and cooperative and had no elicitable tremor.

The urine had a specific gravity of 1.010, a pH of 7, and tests for protein, sugar and acetone were negative. Examination of the blood revealed a hematocrit of 50 per cent and a white cell count of 11,900 per cu. mm. Whole venous blood pH and plasma electrolytes before, during and after the administration of ammonium chloride are recorded in Table 1. The pH determinations were performed in a Cambridge pH meter measured at 38°C. with a glass electrode. Liver function tests performed on admission revealed a bromsulfalein retention of 3 per cent at forty-five minutes, a prothrombin time of 12.0 seconds with a control of 11.7 seconds, and serum alkaline phosphatase of 4.4 Bodansky units. The serum total protein was 6.7; the albumin, 3.5; the globulin, 3.2 gm., and the total bilirubin was 1.4 mg. per cent.

It was believed on admission that the patient had pyloric obstruction due to recurring peptic ulcerative disease and that he was dehydrated and alkalotic from the chronic loss of gastric juice. The azotemia and hypercalcemia were thought to be related to the alkalosis [17].

Initial therapy included administration of calcium carbonate hourly and pamine.[®] The patient continued to vomit large quantities of gastric fluid. Because of the excessive gastric secretions, the decision was made to treat the persistent alkalosis by replacing the gastric chloride loss with ammonium chloride and sodium chloride administered intravenously. Ammonium chloride was administered at a constant rate of approximately 20 mEq. per hour using a continuous twenty-four hour infusion. The fluid and electrolyte therapy was followed-up carefully with balance of intake and output. The pertinent therapy and output volumes are recorded in Table 1.

Late in the first twenty-four hour period of ammonium chloride therapy the patient began to show the tremor of hepatic coma. This consisted of irregular side-to-side movements of the fingers and, with maintenance of posture, the flexion-extension type tremor of the fingers described by Adams and Foley [18]. The tremor was elicited by having the patient maintain a posture of arms outstretched in front of him with extension of the hands at the wrists. An electroencephalogram at this time showed widespread bilateral theta and delta activity.

During the second day of ammonium chloride administration the patient became uncooperative and increasing lethargy, apathy and confusion developed. The tremor occurred in bursts of increasing frequency

TABLE I
SERIAL CLINICAL, BLOOD, URINE AND GASTRIC FLUID CHANGES
IN A PATIENT RECEIVING PARENTERAL AMMONIUM CHLORIDE

Period Ending	2/28-9 A.M.	2/28-3 P.M.	2/29-9 A.M.	3/1-9 A.M.	3/2-9 A.M.	3/3-9 A.M.	3/4-9 A.M.	5/3-9 A.M.
Duration of period (hr.)		6	18	24	24	24	24	24
Therapy (mEq.)								
Ammonium chloride	0	0	375	575	0	0	0	0
Sodium chloride	0	0	300	100	200	600	600	150
Potassium chloride	0	0	0	0	72	240	140	40
Neurologic observations								
Tremor	None	None	Fingers	Upper extremities	None	None	None	None
State of awareness	Normal	Normal	Flat affect, slight slowing of mentation	Drowsy, confused	Normal	Normal	Normal	Normal
Electroencephalogram			Widespread theta and delta activity			Normal		
Blood studies								
Whole blood (pH)	7.60	7.60	7.56	7.56	7.55			7.62
Bicarbonate (mEq./L.)	52	57	46	41	42	38		42
Chloride (mEq./L.)	72	75	86	89	96	108		105
Sodium (mEq./L.)	141	144	138	134	148	149		151
Potassium (mEq./L.)	4.4	3.7	3.7	2.8	3.5	4.2		4.1
Calcium (mg. %)	15.6		14.7	14.9	14.9			13.2
Phosphorus (mg. %)			7.6	3.9	3.7			2.2
Non-protein nitrogen (mg. %)	74		112	129	120	84		55
Arterial ammonia (μ g./%)				210				
Hematocrit	50 (2/27)		42			36		
Urinary excretion								
Volume (ml.)		45	500	1200	1450	2200	3100	3100
Ammonia concentration (mEq./L.)			<1	5	3	8		
Chloride concentration (mEq./L.)		2	6	12	14	62	73	60
Bicarbonate concentration (mEq./L.)			17.0	7.0	16.0			
Sodium concentration (mEq./L.)		19.7	22.7	52.8	49.2			
Potassium concentration (mEq./L.)		93.6	72.8	10.0	24.0			
Calcium (mg./24 hr.)				8.3				37.2
Phosphorus (mg./24 hr.)				3.1				27.9
Nitrogen (gm./24 hr.)		0.2 (6 hr.)	3.0 (18 hr.)	8.3	6.4	12.1	12.4	10.8
Specific gravity			1.010		1.009	1.010	1.009	1.010
Gastric excretion								
Volume (ml.)			1550	4400	1475	2600	2200	3400
Ammonia concentration (mEq./L.)				1	5	5		
Chloride concentration (mEq./L.)			141	139	154	132	155	159
Nitrogen (gm./24 hr.)			2.1 (18 hr.)	1.3	1.1	2.5		
Sodium concentration (mEq./L.)					125			
Potassium concentration (mEq./L.)					8			

and involved not only the fingers but also the wrists, the elbows and the shoulder joints.

With the increase in tremor and mental deterioration, it was feared that coma would ensue if the ammonium chloride therapy were continued. The infusion was therefore discontinued. A total of 950 mEq. (about 50 gm. of ammonium chloride) had been given over a period of forty-two hours. After cessation of the ammonium chloride therapy, the tremor, lethargy and uncooperativeness persisted without noticeable change for about six hours, followed by complete clearing over the next six hours. During the remainder of the hospitalization no tremor of any type was observed.

Approximately six hours after discontinuing ammonium chloride therapy (or forty-eight hours after

the ammonium chloride therapy was begun) the arterial blood ammonia was 210 μ g. and the venous blood ammonia was 124 μ g. per cent by the Conway microdiffusion method [19]. The normal venous range in this laboratory is 30 to 70 μ g. per cent.

As can be seen from Table I, during the administration of ammonium chloride there was a rise in serum non-protein nitrogen from 74 mg. per cent to 112 mg. per cent during the first day, and to 129 mg. per cent during the second day. There were no remarkable alterations in venous pH or plasma calcium which could account for the neurological changes. Liver function tests were repeated on the day after ammonium chloride therapy was discontinued and showed no remarkable change. The bromsulfalein retention was 5 per cent; prothrombin time was

12.6 seconds with a control of 12.6 seconds; the cephalin flocculation test was negative at forty-eight hours and the serum total bilirubin was 0.6 mg. per cent. The serum total protein at this time was 5.5 gm. with an albumin of 2.8 and a globulin of 2.7 gm. per cent.

Urinary and gastric ammonia concentrations as determined by a formal titration method [20] are included in Table 1 and reveal that ammonia was nearly absent in both urine and gastric fluid. These are significant values since the method tends to give high results.

A follow-up electroencephalogram showed "entirely normal patterns of alpha activity only."

On March 8, one week after ammonium chloride therapy, a subtotal gastric resection was performed with alleviation of the pyloric obstruction. The post-operative course was uneventful. A liver biopsy specimen obtained at the laparotomy was grossly and microscopically normal.

In summary, this patient had pyloric obstruction and the accompanying features of alkalosis, hypercalcemia and azotemia which are part of the milk-alkali syndrome as described by Burnett [7]. During intravenous administration of ammonium chloride the mental changes, the arrhythmic flapping tremor and the electroencephalographic abnormality usually seen in hepatic disease developed, but this patient had no evidence of liver disease.

COMMENTS

The relation between the administration of ammonium chloride and the development of the neurologic signs was of interest. Confusion and depressed states of consciousness sometimes are seen in uremia, hypercalcemia, and possibly in alkalosis. These biochemical abnormalities, although present, had no apparent effect on the neurological status of the patient prior to the time of ammonium chloride administration.

The rise in serum non-protein nitrogen that accompanied ammonium chloride therapy was probably due to the nitrogen load in the presence of impaired renal function. It is unlikely that the rise in non-protein nitrogen caused the neurologic signs because there was rapid clinical improvement after stopping the ammonium chloride even though the non-protein nitrogen remained elevated. It seems likely, therefore, that the neurologic signs were precipitated by the administration of ammonium chloride. The finding of an elevated blood ammonia six hours after discontinuing the infusion also correlates with the persistence of the neurologic signs six to twelve hours after the administration of the ammonium chloride was discontinued.

The tremor was identical with the tremor of

hepatic coma [18] in that it was brought on by sustained effort such as maintenance of posture; it occurred in bursts of increasing frequency when the muscular tension was sustained. The tremor had a quick release (flexion) and a slightly slower restitution to the original posture, giving the appearance of flapping, and it was bilaterally asymmetric. The tremor, therefore, would not be confused with other types such as the intention tremor. Except when the patient was unable to cooperate because of lethargy, the tremor was an easy sign to observe and follow.

Venous infusion of ammonium chloride introduces the ammonium directly into the systemic circulation and thus bypasses the liver. In this situation a normal liver does not first have the opportunity of clearing the blood of ammonia; this could be considered analogous to the "portosystemic syndrome" in which an Eck fistula or liver disease allows ammonia in the portal system to enter the systemic circulation.

As intravenous administration of ammonium chloride has been a form of therapy for some years, it is difficult to explain why neurologic signs have not been observed frequently during rapid or prolonged administration. Another factor in this case may have contributed: (1) The dose of ammonium chloride, although inadequate to correct the alkalosis, was quite large and may have exceeded the normal ability of this individual to utilize ammonia. (2) Although by all available criteria the patient's liver appeared normal, a functional impairment not detected by the methods used could have been present [21]. (3) Alkalosis, *per se*, may augment the appearance of neurologic signs due to ammonia [22]. It has been suggested that an increased partial pressure of ammonia due to alkalosis may contribute to the appearance of the signs of ammonia toxicity. (4) An intrinsic mechanism other than the liver which operates in clearing the systemic circulation of ammonia might have been impaired. Evidence for such a defect is lacking as the large arterial-venous ammonia difference in this patient demonstrates the usual "uptake" of ammonia by muscle [23]. (5) The brain may be more sensitive to a level of circulating ammonia in the presence of a high blood urea. (6) Alkalosis, by inhibiting urinary ammonia excretion, may have accentuated the accumulation of ammonia in the blood of this patient. However, it is not clear at present whether or not urinary excretion of

ammonia plays a role in the removal of ammonia from the blood.

SUMMARY

While on intravenous ammonium chloride therapy, the flapping tremor, mental apathy and confusion, and electroencephalographic changes seen in hepatic coma developed in a patient with severe alkalosis and the "milk-alkali syndrome." Hepatic tests and liver biopsy were normal. The symptoms were attributed to the toxic effects of ammonia on the central nervous system. This is interpreted as further evidence that the symptoms of hepatic coma are due to ammonia.

Acknowledgment: The authors appreciate the helpful suggestions of Dr. Charles S. Davidson, Boston, Massachusetts, of Drs. Thomas B. Connor and Theodore E. Woodward, Baltimore, Maryland, and of Dr. James Burnell, Seattle, Washington, in preparation of this manuscript.

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Portal Hypertension and Bleeding Esophageal Varices Secondary to Sarcoidosis of the Liver*

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RECENTLY attention has been called to the fact that gastrointestinal hemorrhage should be included among the protean manifestations of sarcoidosis. Blum and Mitchell reported a case of massive gastrointestinal hemorrhage in a patient with hypersplenism and thrombocytopenia secondary to sarcoidosis [1]. The bleeding was thought to be due to the thrombocytopenia and no intrinsic gastrointestinal lesion was found at necropsy. McKusick presented a case of massive gastrointestinal hemorrhage secondary to sarcoid involvement of the gastric mucosa and secondary superficial ulceration [2]. Brick and Jeghers mentioned a case of massive hematemesis in a sarcoid patient in whom there was roentgenographic evidence of a prepyloric ulcer [3]; they were, however, unable to establish a definite relationship of the patient's underlying disease to his gastric ulcer and bleeding episode. Klatskin mentioned a case of severe sarcoidosis of the liver with secondary portal hypertension, esophageal varices and gastrointestinal hemorrhage [4]. The patient was treated with a surgical shunting procedure.

The following case represents a similar problem and is thought to be the second reported in which gastrointestinal hemorrhage occurred from esophageal varices secondary to sarcoidosis of the liver.

CASE REPORT

J. B., a thirty-eight year old white man, was first admitted to the Veterans Administration Hospital, Philadelphia, in November, 1955. In 1950 he had been hospitalized in another institution for a febrile illness. At that time slight hepatomegaly was noted and there was laboratory evidence of impairment of hepatic function. He had a bromsulphalein® retention of 20 per cent in forty-five minutes, a 3 plus cephalin flocculation test in forty-eight hours and a 40 per cent prothrombin time. There was no evidence of hyper-

bilirubinemia at that time and other studies performed were within normal limits, including a heterophil agglutination test and a complement fixation test for brucellosis. Following that episode the patient was essentially asymptomatic until one month prior to his admission to this institution at which time he had a brief illness characterized by fever, chills and malaise. He had had several formed tarry stools unaccompanied by hematemesis.

One week prior to admission he again had melena, associated with marked weakness. The patient's alcohol consumption was limited to one glass of beer per day. The remainder of his past and family history was non-contributory.

Physical examination on admission revealed a well developed and nourished, acutely ill white man with marked pallor. There was no clinical evidence of icterus. His blood pressure was 120/70 mm. Hg; pulse, 80; respirations, 12; temperature, 99°F. Examination of the head, eyes, ears, nose, throat, heart and lungs was within normal limits. The liver was felt 2 cm. below the right costal margin and the spleen was palpable 1 cm. below the left costal margin. The remainder of the physical examination was within normal limits except for minimal pitting pretibial edema.

Laboratory studies revealed an initial hemoglobin of 5.5 gm. per cent. The hematocrit was 18 per cent; white blood count, 2700 per cu. mm. with 64 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes and 2 per cent eosinophils. A urinalysis was within normal limits. The blood urea nitrogen was 12 mg. per cent; fasting blood sugar, 114 mg. per cent. The serum bilirubin was 1.2 mg. per cent, with 0.2 mg. direct and 1.0 mg. indirect. The serum alkaline phosphatase was 3 Shinawara units; prothrombin time, 40 per cent of normal; cephalin flocculation test, 2 plus in forty-eight hours; thymol turbidity, 5 units; and thymol flocculation, 1 plus. The serum total proteins were 6.4 gm. per cent with 3.2 gm. of albumin and 3.4 gm. of globulin. There was 11.5 per cent retention of bromsulphalein in forty-five minutes using 5 mg. of the dye per kilogram of body weight. The urinary urobilinogen was 0.7 Ehrlich units per twenty-four hours. The Coombs' test was

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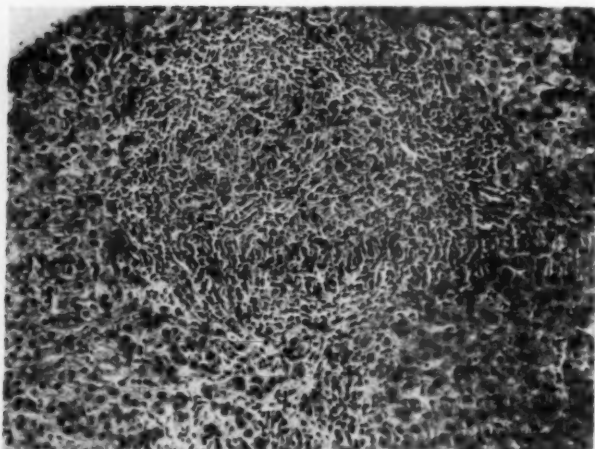


FIG. 1. Photomicrograph of liver showing granulomatous lesion. Original magnification, $\times 110$.

negative in both indirect and direct phases. An electrocardiogram and chest roentgenogram were within normal limits.

Conventional ulcer therapy was instituted and blood transfusions were given. There was no further evidence of gastrointestinal hemorrhage. Roentgenograms of the upper gastrointestinal tract revealed esophageal varices; the stomach and duodenum appeared to be normal. The presence of varices was confirmed by a repeat barium study and by esophagography. Serial hemograms revealed a persistent thrombocytopenia with a platelet count ranging from 58,000 to 80,000 per cu. mm. Clot retraction was poor and a Rumpel-Leede's test was positive. Leukopenia below 4,000 also persisted. Because of the evidence of portal hypertension and hypersplenism it was considered that splenectomy and a spleno-renal shunt were indicated. At the time of surgery the liver was found to be enlarged and had an irregular hobnailed surface. The spleen appeared to be three to four times its normal size. The portal pressure on direct measurement was 360 ml. of water. Due to technical reasons the spleno-renal shunt could not be performed. A splenectomy was carried out and abdominal lymph node and liver biopsies were performed. Microscopic sections of the spleen, lymph node and liver revealed diffuse granulomatous infiltration. (Fig. 1.) The granulomas were composed of large epithelioid cells with granular eosinophilic cytoplasm. Many of the nodules showed associated giant cells of the Langhans' type. There was no evidence of central necrosis, caseation or perinodular inflammation.

The patient's postoperative course was uneventful. There was an immediate postoperative rise in the platelet count to 410,000 per cu. mm. and the white blood cell count returned to normal limits.

The patient was admitted again in April 1956 at which time he gave a history of recurrent melena for a three-day interval one month prior to his readmission. Except for the presence of a well-healed transverse abdominal scar and 2 cm. enlargement of the liver,

the physical examination was within normal limits. The hemoglobin was 11.7 gm. per cent; hematocrit, 42 per cent; reticulocyte count, 4.8 per cent; and platelet count, 398,000 per cu. mm. The blood urea nitrogen was 13 mg. per cent. The serum total proteins were 7.5 gm. per cent of which 3.7 gm. was albumin, 3.8 gm. globulin. There was 13.5 per cent bromsulphalein retention in forty-five minutes. Urinalysis and a serological test for syphilis were negative. Skin tests for histoplasmin and coccidioidin, and a first strength P.P.D. test were negative; a second strength P.P.D. test was positive. Upper gastrointestinal roentgenogram revealed the persistence of esophageal varices. There was no evidence of intrinsic disease in the stomach and duodenum.

Because of the second episode of gastrointestinal hemorrhage the patient was prepared for a prophylactic portacaval shunt. At the time of the patient's second operation there were numerous large lymph nodes along the course of the portal vein. The liver had the same enlarged, hobnailed appearance. The portal vein pressure was 320 ml. of saline solution compared to 120 ml. in the inferior vena cava. A portacaval anastomosis was performed, together with lymph node and liver biopsy. The patient did well postoperatively and roentgenographic examination of the upper gastrointestinal tract three weeks later revealed an apparent disappearance of the previously noted esophageal varices. Cultures of the abdominal lymph nodes and liver specimen were negative for tuberculosis or brucella organisms. The biopsies appeared similar to those obtained at the first operation.

The patient has been observed ten months following the portacaval shunt and has been asymptomatic. He has had no further evidence of gastrointestinal hemorrhage. There has been no roentgenographic evidence to date to suggest involvement of any other organs by sarcoidosis.

COMMENTS

Involvement of the liver in sarcoidosis has been recognized for a long time and the frequency of hepatic sarcoidosis is now widely appreciated. In an autopsy series of 607 cases of Boeck's sarcoid, there was hepatic involvement in 66.5 per cent [5]. In only 19 per cent of these cases, however, had involvement of the liver been suspected clinically. Other series have reported a frequency of hepatic sarcoidosis of between 63 and 76 per cent [5-7]. Branson and Park estimate that 2 per cent of all liver disease is due to sarcoidosis [6]. The increasing use of needle biopsy of the liver has rendered it a valuable tool in the diagnosis of sarcoidosis. Care must be taken, however, in differentiating the specimen obtained at liver biopsy from tuber-

culosis and non-caseating granulomatous diseases due to fungi, brucellosis and berylliosis. Hepatomegaly of itself is no infallible criterion of hepatic sarcoidosis since this may occur secondary to cor pulmonale and congestion.

Despite the frequency of demonstrable microscopic involvement of the liver by Boeck's sarcoid, significant disturbances of hepatic function have rarely been described [8]. Until the case reported by Branson and Park in which death occurred due to hepatic insufficiency secondary to sarcoidosis, this disease had not been considered to be a cause of liver failure. Although jaundice has been reported in association with hepatic sarcoidosis, it is rare [9-14]. In many of the reported cases the relationship of jaundice to the underlying sarcoidosis has not been clear. The exact mechanism of jaundice is debatable. Some have attributed it to pressure on the portal triads by the granulomatous lesions and the destruction of hepatic architecture and extensive fibrosis. Others have attributed icterus to extrinsic pressure caused by enlarged lymph nodes at the porta hepatis.

Ascites is a rare complication of sarcoidosis [5,6,15]. In one instance it has been attributed to portal hypertension; in this case a striking infiltration of the walls of several of the larger hepatic sublobular veins was reported [15]. Cirrhosis or a cirrhosis-like picture of the liver is rarely found. Klatskin has reported that the increased periportal fibrosis and disruption of the lobular architecture by the granulomatous lesions could lead to cirrhosis during the phase of healing [5].

In the patient herein reported focal non-caseating granulomas of the liver, spleen and abdominal lymph nodes were found. It was considered that other entities, such as tuberculosis, brucellosis, berylliosis and fungus diseases, had been adequately excluded by the history, negative skin tests and antigen titers, negative blood cultures and negative tissue cultures. The hepatic involvement was of such severity that on two occasions the portal pressure was elevated on direct measurement. The episodes of gastrointestinal hemorrhage must be attributed to the esophageal varices which were visualized both roentgenographically and by esophagoscopy. Repeated roentgenographic examinations did not demonstrate evidence of other gastrointestinal pathologic conditions. The possible etiologic role of thrombocytopenia as a cause of the bleeding seems to have been ruled out by its

correction following splenectomy. Following the patient's portacaval shunt, roentgenograms of the esophagus revealed that the varices had disappeared. The patient has been asymptomatic for ten months following the operation and there has been no evidence of gastrointestinal bleeding.

SUMMARY

A case of sarcoidosis manifested by gastrointestinal hemorrhage is presented. The bleeding is believed to have originated from esophageal varices secondary to hepatic sarcoidosis and portal hypertension. The patient improved following portacaval anastomosis.

The literature relating to the incidence of gastrointestinal hemorrhage in sarcoidosis and the mechanisms by which it may occur are reviewed.

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Herpes Zoster with Ileus Simulating Intestinal Obstruction*

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HERPES zoster may, on occasion, result in a symptom complex highly suggestive of acute intestinal obstruction. Reference to this situation has been made in the foreign literature by Chene and Gisselbrecht [3] and Reifferscheid [7]. These authors have properly indicated the necessity for recognizing the presence of ileus in certain cases of herpes zoster in order to avoid unnecessary surgery.

We recently had occasion to study a patient with known herpes zoster in whom signs and symptoms suggesting intestinal obstruction developed, and in addition demonstrated roentgen findings on a survey film of the abdomen consistent with an obstructive process in the left colon. A barium enema study revealed a long, smoothly constricted area in the mid-sigmoid partially impeding the passage of the enema. Proper roentgen evaluation of the changes in the sigmoid suggesting an inflammatory and/or spastic condition resulted in conservative management of this patient without resort to surgery which was seriously contemplated at that time.

This case is unique in that the barium enema demonstrated a localized, spastic inflammatory change in the sigmoid. None of the other cases reported in the literature, in which enema studies were performed, demonstrated any abnormality [3].

It is also interesting that the pathologic changes in the sigmoid disappeared slowly, the bowel finally assuming a completely normal appearance as evidenced by progress enema studies. There was concomitant improvement in the clinical condition of this patient.

CASE REPORT

C. C., a sixty-five year old white woman, was admitted to the Grace Hospital on September 7, 1951 with the chief complaint of "shingles," pain in the back, abdominal distention, pain and constipation.

The present illness began approximately one week before with sudden onset of pain in the back radiating anteriorly to the abdomen. The patient noted vesicle formation and some crusting of the skin in the area of involvement. She suffered from severe constipation and took laxatives regularly. She noted "bloating," some abdominal distention and no bowel movements during the present illness.

The past history was essentially negative. Menopause began at age forty-five with no difficulties in this regard.

Physical examination revealed a well developed and well nourished woman who appeared chronically ill. The abdomen was distended and diffusely tender. No palpable masses were discovered. Peristaltic sounds were audible. A vesicular rash with a tendency to coalescence and crusting in localized areas was seen to extend around the abdomen at the approximate levels of L1 and L2 on the left side. The distribution of the lesion seemed to follow the pathway of the eighth and ninth thoracic nerves. There was tenderness in both costovertebral angle areas. Otherwise, the physical examination revealed no abnormalities.

A scout film of the abdomen taken on the day following admission revealed fairly marked gaseous distention of the ascending and transverse colon, with minimal distention of small bowel loops. The pattern was deemed consistent with obstruction of the left colon and a barium enema was advised. (Fig. 1.) This was administered immediately and revealed a smoothly margined constricted area in the mid-sigmoid without serious impediment to the passage of barium. (Figs. 2A and B.) After reviewing the films the impression was that we were dealing with some type of inflammatory or localized spastic colitis, possibly neurogenic in origin. In view of this opinion, surgery was deferred and conservative management was instituted. A laxative was given and the patient moved her bowels with almost complete expulsion of the barium mixture. The patient felt improved at this time, with decrease in abdominal distention.

On September 9, a sigmoidoscopic examination was carried out, the tube being passed 20 cm. No pathologic condition was discovered. On September

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FIG. 1. Scout film of the abdomen showing moderately severe distention of the ascending and transverse colon, with minimal distention of distal small bowel. The findings were considered to be consistent with obstruction of the left colon.

12 a barium enema was repeated and marked improvement in the appearance of the bowel was noted. There was still some evidence of mild spasm, although the concentric deformity previously noted was not observed. (Fig. 2C.)

The clinical picture was one of marked over-all improvement and the patient was discharged on September 17. On October 11, 1951 the patient returned as an out-patient and a barium enema demonstrated completely normal findings in the colon. The sigmoid was completely distensible, showed normal haustrations and no pathologic changes of any type. (Fig. 2D.)

COMMENTS

The first significant observations relating to the pathogenesis of herpes zoster are generally accredited to von Baerensprung [7] who by post-mortem observations established association of the segmental cutaneous eruption with a lesion of the segmental dorsal root ganglion. This association was substantiated by the extensive observations of Head and Campbell [4].

Inoculation experiments of Kundralitz [5] and other investigators suggested that the skin was not the point of entry in herpes zoster. In their

experiments intradermal injection of vesicle fluid from cases of herpes zoster did not produce the entire picture of zoster, i.e., segmental neuralgia followed by a belt of vesicles, but resulted in local vesiculation only. Other workers have attributed the rash to vasomotor phenomena secondary to involvement of the dorsal root ganglia.

The portal of entry and the means by which the virus gains access to the dorsal root ganglia have not been established. However, Cheatham [2] recently published autopsy data in a case of herpes zoster with a varicelliform eruption in which intranuclear inclusion bodies were demonstrated within the esophageal mucosa, myenteric plexus of the stomach, dorsal root ganglia, and a sympathetic ganglion at the level of the affected dorsal root ganglia. In addition, similar intranuclear inclusions associated with focal necrosis were seen within cells in lesions of the pancreas, adrenal glands and one ovary. Cheatham concluded that the respiratory and gastrointestinal tracts probably served as portals of entry in most cases of herpes zoster.

It is postulated by others that the virus enters the body via the sympathetic nerves of the esophagus and migrates by way of the sympathetic nerves to the dorsal root ganglia, eventually reaching the skin by centrifugal spread along the respective peripheral nerves. Schirduan and Dietze [6] recently reported a case in which the virus had caused inflammatory changes in the sympathetic and parasympathetic ganglia as well as in the wall of the terminal ileum.

Clinically it is of interest that in the cases of herpes zoster with ileus discussed by Chene and Gisselbrecht [3], and also in our case, the skin manifestations were localized to the lower left hemithorax, in the distribution of the eighth, ninth (and occasionally in the tenth) thoracic interspaces. It is also significant that in two of their three cases, no abnormality was demonstrated on barium enema study [3].

It is not known in our case, which demonstrated inflammatory and/or spastic changes in the sigmoid on barium enema study, whether these changes were due to reflex, segmental spasm due to involvement of the autonomic system or whether there was direct involvement of the sigmoid by the herpes virus. On a physiologic basis it would appear inconceivable that spasm due to reflex irritation of postganglionic components of the sympathetic system would account for such a change, since in this portion of

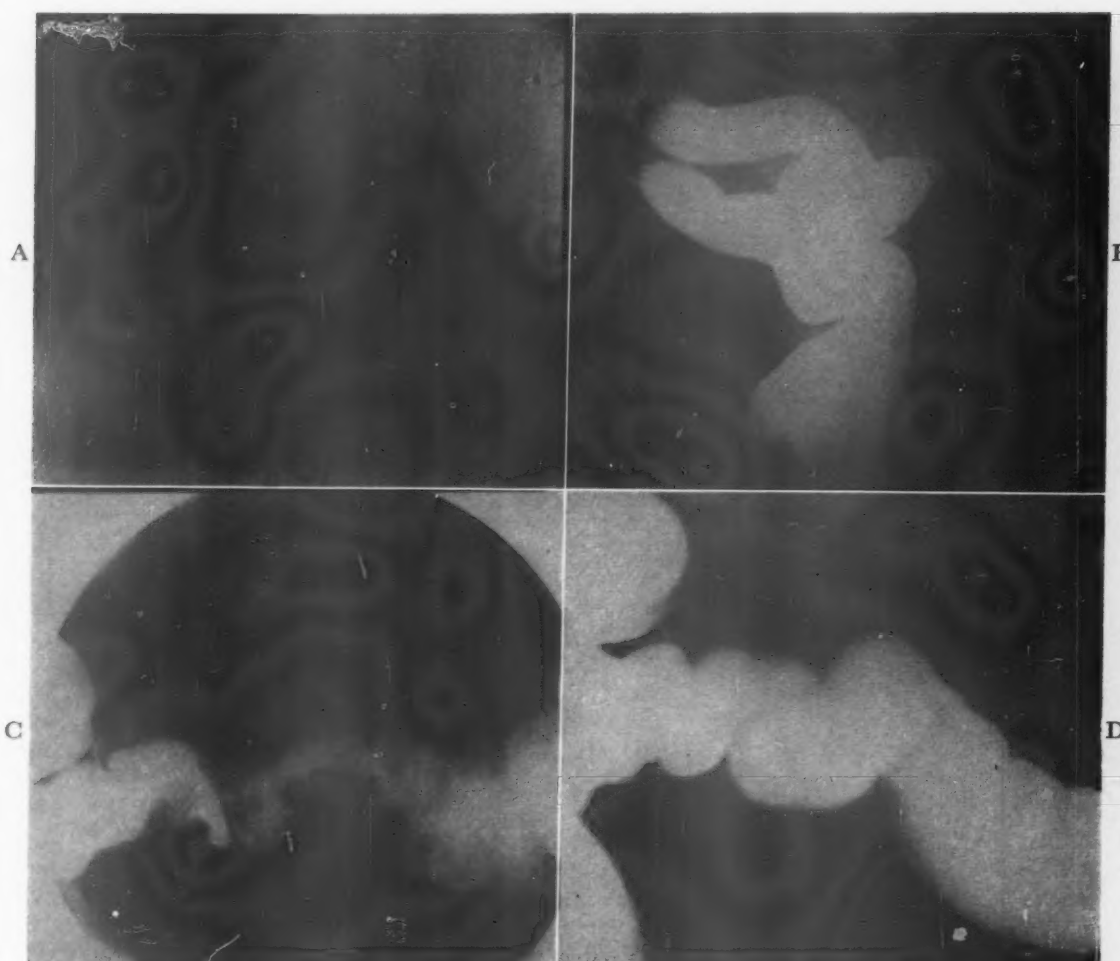


FIG. 2. A and B, pre- and postexpulsion barium enema films demonstrating smoothly margined, concentric defect in the sigmoid. C, repeat study four days later showing marked improvement in the appearance of the bowel. D, barium enema one month after the initial examination demonstrates normal findings.

the bowel increased tonus is a function of the parasympathetics and there is no possible anatomic correlation between the level of skin involvement and a sigmoid lesion such as was demonstrated in our case. It may well be, therefore, that in our case the pathologic changes in the sigmoid were an expression or manifestation of direct involvement of this colonic segment by the herpes virus. It is not known whether such involvement is due to direct invasion of the mucosa or to passage of herpes virus along the sympathetic postganglionics to the sigmoid.

SUMMARY

1. A case of herpes zoster with ileus simulating intestinal obstruction is presented in which barium enema studies demonstrated a constant, smooth constriction in the sigmoid colon which subsequently returned to normal.

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2. The necessity for accurate evaluation of the roentgen changes in the barium enema studies is stressed. The possibility of intestinal involvement in herpes zoster should be kept in mind in order to obviate undesirable and unnecessary surgical intervention in such cases.

3. It is believed in our case that the pathologic changes in the sigmoid on barium enema study may have been due to direct involvement of the sigmoid by the herpes virus, since these changes cannot be satisfactorily accounted for on the basis of reflex segmental spasm.

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The American Journal of Medicine

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Volume XXIII
JULY TO DECEMBER

1957

THE AMERICAN JOURNAL OF MEDICINE, INC.

NEW YORK

MCMLVII

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Printed in the United States of America

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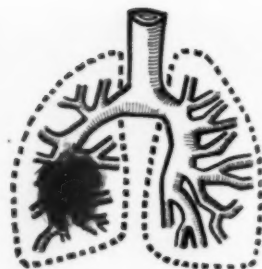
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DIVISION OF HOFFMANN-LA ROCHE INC
Nutley 10 • New Jersey

THE TRAIL PATIENT

On
the
go...



**an advanced method of
theophylline therapy**

CLYSMATHANE

(FLEET)

Disposable Rectal Unit

simple...safe...effective...

For the alleviation of symptoms in bronchial asthma and the acute episodes of heart failure, CLYSMATHANE (Fleet) supplies prompt therapeutically adequate blood levels of theophylline.⁽¹⁾

Even after repeated dosage CLYSMATHANE (Fleet) minimizes the side effects often associated with oral or parenteral theophylline administration. The plastic squeeze bottle (with attached, prelubricated, non-traumatic rectal tube) is designed for self-administration.

Dosage: One CLYSMATHANE (Fleet) Unit as a retention enema before retiring or as directed. Available on prescription at professional pharmacies.

Composition: Theophylline monoethanolamine (Theamin, Fleet) 0.625 Gm. aqua 37.0 ml. in rectal dispenser. Units packed in individual cartons, manufacturer's label readily removable.

REFERENCE: (1) Ridolfo, A. S. & Kohlstaedt, K. G., "A simplified method for the rectal instillation of theophylline"—to be published



CLYSMATHANE

(FLEET)

Disposable Rectal Unit



Professional Samples and literature on request

C. B. FLEET CO., INC.

Lynchburg, Virginia

THE TRAIL PATIENT



on
the
mend...

WHEN HER SWEET TOOTH TROUBLES HER DIGESTION

TAKA-COMBEX®



to help her cope with carbohydrates
avoid vitamin deficiencies

*TAKA-COMBEX Kapseals®—containing
the starch-digestant Taka-Diastase®,
B vitamins, ascorbic acid, and liver concentrates—
are available in bottles of 100 and 1,000.*

*TAKA-COMBEX Elixir—containing Taka-Diastase
and B vitamins—is available in 16-ounce bottles.*

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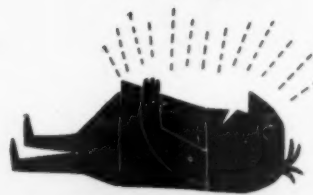
NOSE COLD



HEAD COLD



ASIATIC
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PHENAPHEN® PLUS

Phenaphen Plus is the physician-requested
combination of Phenaphen, plus an anti-
histaminic and a nasal decongestant.



Available on prescription only.

each coated tablet contains: **Phenaphen**

Phenacetin (3 gr.)	194.0 mg.
Acetylsalicylic Acid (2½ gr.)	162.0 mg.
Phenobarbital (¼ gr.)	16.2 mg.
Hyoscyamine Sulfate	0.031 mg.

plus

Propenpyridamine Maleate	12.5 mg.
Phenylephrine Hydrochloride	10.0 mg.



THE TRAL PATIENT

unbothered
by the
ulcer
or the
medicine

marked selectivity in anticholinergic therapy

FILMTAB **TRAL***

*TRAL—TRADEMARK

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(HEXOCYCLUM METHYLSULFATE, ABBOTT) Abbott

CLINICAL COLLOQUY

My patients complain that
the effect of the pain tablet I prescribe
often wears off in less than 3 hours.

*Why not try the new analgesic
that gives faster,
longer-lasting pain relief?*

You mean something that
doesn't require repeat dosage so often?

*Yes—it's called Percodan.[®]
It not only works in 5 to 15 minutes but
one tablet sustains its pain-relieving effect
for 6 hours or longer!*

How about side effects?

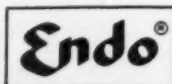
*No problem. For example,
the incidence of constipation
is rare with Percodan.**

Sounds worth trying—what's the average adult dose?

One tablet every 6 hours. That's all.

Where can I get literature on Percodan?

Just ask your Endo detailman or write to:

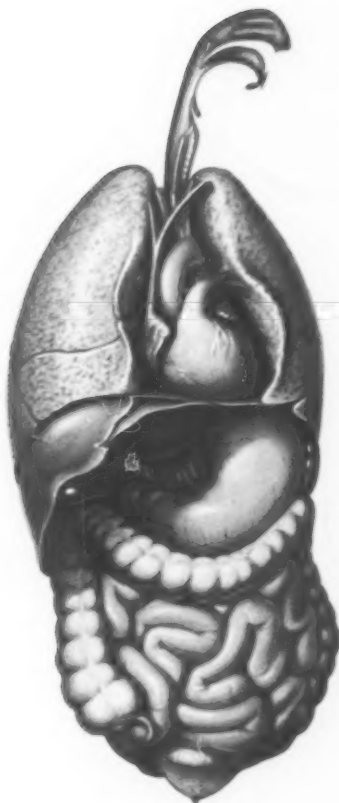


ENDO LABORATORIES

Richmond Hill 18, New York

*U.S. Pat. 2,628,185. PERCODAN contains salts of dihydrohydroxycodone and homatropine, plus APC. May be habit-forming. Available through all pharmacies.

**INTENSIFIED
BROAD-SPECTRUM
ANTIBIOTIC
CONTROL**



*often the difference
between rapid and
delayed response*

Tetrex®

Tetracycline Phosphate Complex

CAPSULES

“absorption with tetracycline phosphate complex [TETREX] is about twice as efficient as that obtained with tetracycline hydrochloride”¹

practically sodium-free pure compound—*not a mixture*—freely indicated in low-sodium regimens



*DUANAT® REPRODUCTION. PAT. PENDING.

now toward
"saturation control"
in urinary
tract infection



plus analgesia

AzotrexTM

CAPSULES

*intensified tetracycline control with TETREX
potentiated in anti-infective concentration
and range by sulfamethizole — outstanding
sulfonamide for solubility, absorption, safety
plus the remarkably rapid and specific g.u.
analgesic action of phenylazo-diamino-
pyridine HCl in dysuria, frequency and urgency*

Each AZOTREX Capsule contains:

TETREX (tetracycline phosphate complex) . . . 125 mg.
(tetracycline HCl activity)
Sulfamethizole 250 mg.
Phenylazo-diamino-pyridine HCl 50 mg.

Minimum adult dose: One capsule q. i. d.

Supplied: Bottles of 24 capsules



DUANAT REPRODUCTION. PAT. PENDING.

INTENSIFIED
BROAD-SPECTRUM
ANTIBIOTIC
CONTROL

Tetrex®

Tetracycline Phosphate Complex

CAPSULES

*To the point
of infection
as in septicemia*

*often the difference
between rapid and
delayed response*

*blood levels practically double those of
tetracycline hydrochloride within 1-3
hours/maintains higher blood levels
than tetracycline hydrochloride up
to 24 hours/a single, highly efficient
antibiotic permitting simple, flexible
dosage/equally effective on convenient
b.i.d. schedule, as on a q.i.d. schedule
/practically sodium-free—pure com-
pound—not a mixture.*



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Supplied: TETREX Capsules containing the equivalent of 250 mg. tetracycline HCl activity; bottles of 16 and 100. New TETREX Pediatric Capsules containing the equivalent of 100 mg. tetracycline HCl activity; bottles of 25 and 100.

**INTENSIFIED
TETRACYCLINE
CONTROL**

new for respiratory infections



Integrated with

ANALGESIA CONTROL

ANTIHISTAMINE CONTROL

*The only anti-infective
preparation*

*providing "all-factor"
control through the*

*(1) faster, higher blood
levels and broad-range activity
of TETREX (2) analgesic-antipyretic
action of APC (3) notably potent
antihistamine effects of BRISTAMIN,
virtually free of somnolence.*

*Specific therapy for bacterial infections
caused by tetracycline-sensitive
organisms. Ideal adjunctive therapy
in common respiratory infections
for control of secondary
bacterial invasion.*

Convenient, economical.

Each capsule contains:

TETREX (tetracycline phosphate complex) 125 mg.
(tetracycline HCl activity)

Aspirin	150 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Bristamin (Phenyltoloxamine Citrate)	25 mg.

Usual dose: One or two capsules q.i.d.

Supplied: Bottles of 24



Tetrex-APC
WITH BRISTAMIN®

*DUANAT® REPRODUCTION. PAT. PENDING.

ENOVID*

BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER

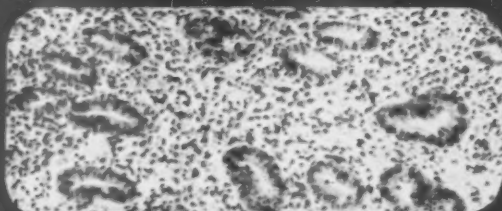
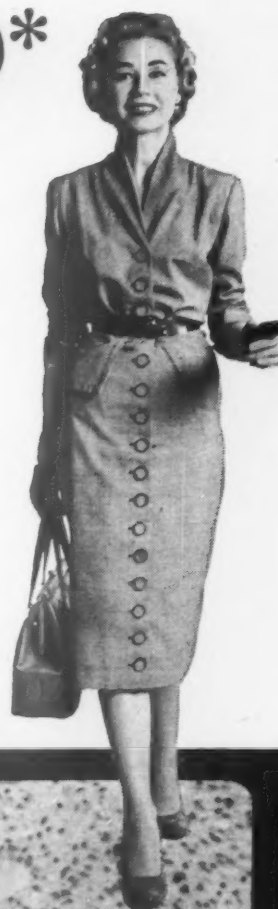
Regulates menstrual disorders through reliable endometropic control

Enovid is Searle's new, orally effective agent designed to provide specific control of menstrual disorders.

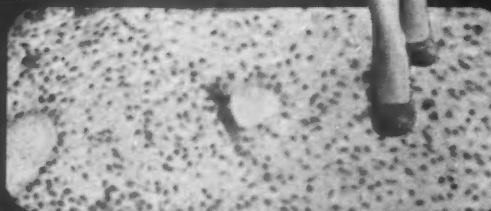
Enovid contains norethynodrel, a new synthetic steroid with strong progestational and lesser estrogenic activity. The estrogenic effect, enhanced by the addition of ethynylestradiol 3-methyl ether, prevents spotting or breakthrough bleeding in most patients in whom it would otherwise occur.

Like the normal endocrine action of the corpus luteum, Enovid maintains the integrity of the endometrium during administration of the drug. Moreover, as occurs on withdrawal of the natural hormone, the withdrawal of Enovid results in the flow characteristic of menstruation. Also, as does the natural hormone, Enovid controls the gonadotropic functions of the anterior pituitary glands.

This specific control of the menstrual cycle permits effective treatment of both excessive and inadequate endometrial activity and provides the physician with a dependable agent for treating such disorders as amenorrhea, dysmenorrhea, menorrhagia, metrorrhagia and premenstrual tension.



Pretreatment biopsy from patient with anovulatory menometrorrhagia.
Interpretation: Proliferative endometrium



Post-treatment biopsy on day 25 after 10 mg. of Enovid daily from day 5 to day 20.
Interpretation: Late secretory endometrium with pseudo-decidual stromal development.

Biopsy photomicrographs courtesy of Anna L. Southam, M.D., New York, N.Y.

INDICATIONS AND DOSAGE GUIDE FOR ENOVID		
DISORDER	FIRST CYCLE	SECOND AND THIRD CONSECUTIVE CYCLES
Menorrhagia	One or two 10-mg. tablets daily to day 25 of the cycle.	One 10-mg. tablet daily from day 5 to day 25*
Metrorrhagia	One or two 10-mg. tablets daily to day 25 (or for 10 days to establish cycle)	same as above
Amenorrhea (primary or secondary)	One 10-mg. tablet daily for 20 days to establish cycle	same as above
Oligomenorrhea	One 10-mg. tablet daily from day 5 to day 25*	same as above
Premenstrual Tension	One 10-mg. tablet daily from day 5 to day 25*	same as above
Dysmenorrhea	One 10-mg. tablet daily from day 5 to day 25	One 10-mg. tablet daily from day 5 to day 25
Inadequate Luteal Phase	One 10-mg. tablet daily from day 15 to day 25	One 10-mg. tablet daily from day 15 to day 25

*The administration of Enovid prior to day 15 may interfere with ovulation; if anovulatory cycles are not desired, one 10-mg. tablet of Enovid should be administered daily from day 15 to day 25.

SPECIAL NOTES: (1) If nausea is encountered, the daily dose may be cut in half or given in divided doses for three days and then return to regular dose. (2) Intermenstrual spotting is usually evidence of inadequate dosage. This type of bleeding is usually controlled by increasing the dosage one 10-mg. tablet daily. (3) Follow-

ing discontinuance of treatment, the intermenstrual interval of the first untreated cycle is commonly prolonged for approximately one week.

FORMULA: Each 10-mg. tablet of Enovid (available as uncoated, scored, coral tablets) contains norethynodrel, a new synthetic steroid, with 0.15 mg. of ethynylestradiol 3-methyl ether.

*Trademark of G. D. Searle & Co.

G. D. Searle & Co., Chicago 80, Illinois

SEARLE

Research in the Service of Medicine

for the depressed and regressed
selective increase in psychic energy
MARSILID

(iproniazid)

Roche

In both mild and severe depression, Marsilid can restore a sense of healthy well-being, with renewed vigor, activity and interests. Patients with acute depression refractory to shock treatment have shown a heartening response to Marsilid. Even "burned out" psychotics, untouched by any other therapy, have become more alert, responsive and sociable.

As a psychic energizer, Marsilid is truly unique. It provides continuous mood improvement with gradually reduced dosage. Patients do not develop resistance to its normalizing effect; there is no tachyphylaxis. Marsilid does not elevate blood pressure . . . does not decrease but usually stimulates appetite.

In mild depression, improvement with Marsilid is usually evident within a week or two. In severe depressive states of hospitalized psychotics, a month or more may be required for apparent response . . . but Marsilid often leads to complete remission, obviating the need for shock therapy.

Note: Marsilid is contraindicated in patients who are agitated, overactive or overstimulated, or in those with a history of renal or hepatic disease.

For complete references and information concerning dosage, indications and contraindications, write V. D. Mattia, Jr., M. D., Director of Medical Information, Roche Laboratories, Division of Hoffmann-La Roche Inc, Nutley 10, N. J.

MARSILID® PHOSPHATE — brand of iproniazid phosphate

Supplied in scored tablets of 50 mg (yellow), 25 mg (orange), and 10 mg (pink)



Original Research in Medicine and Chemistry

NEW...

*A more potent,
more effective,
lower-dose antidiarrheal*

With a powerful new adsorbent—having five times the adsorbent action of kaolin

With two synergistic antibiotics—having a more effective antidiarrheal spectrum (with systemic absorption so minimal as to preclude toxicity)

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With refreshing taste—for acceptability in all age groups



Polymagma^{*}

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Peftin with Cloquore[®] (Gelatinated Atropazine, Wyeth) in Alumina Gel



Philadelphia 1, Pa.

Supplied: Bottles of 8 fl. oz.

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with all other foods

For nutrition...protein...energy...
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For texture...nonirritant...neither chemically
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For low fat content...when fat must be restricted

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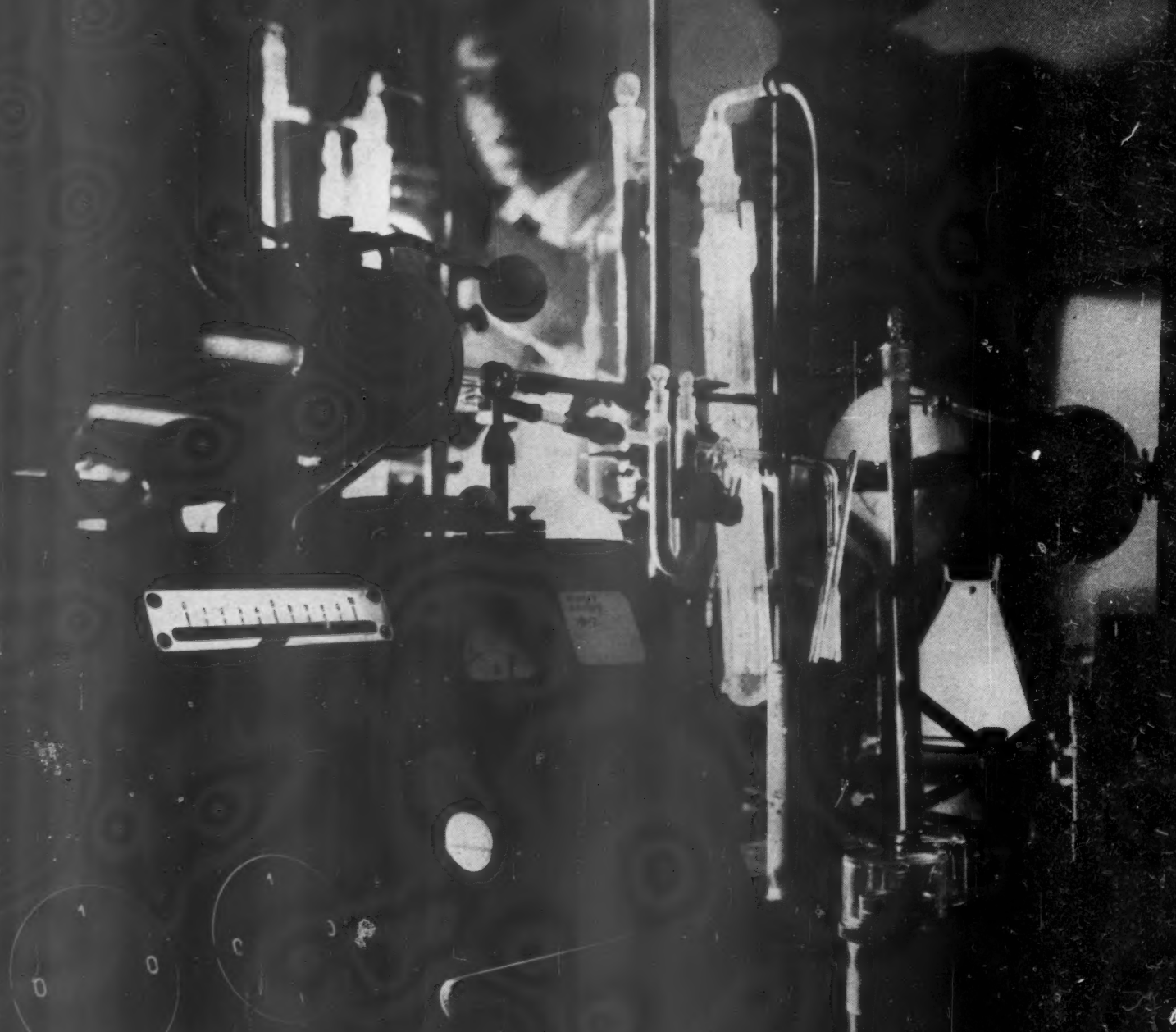


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Enriched Bread helps supply
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always compatible.

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Creating a major drug with great new promise*

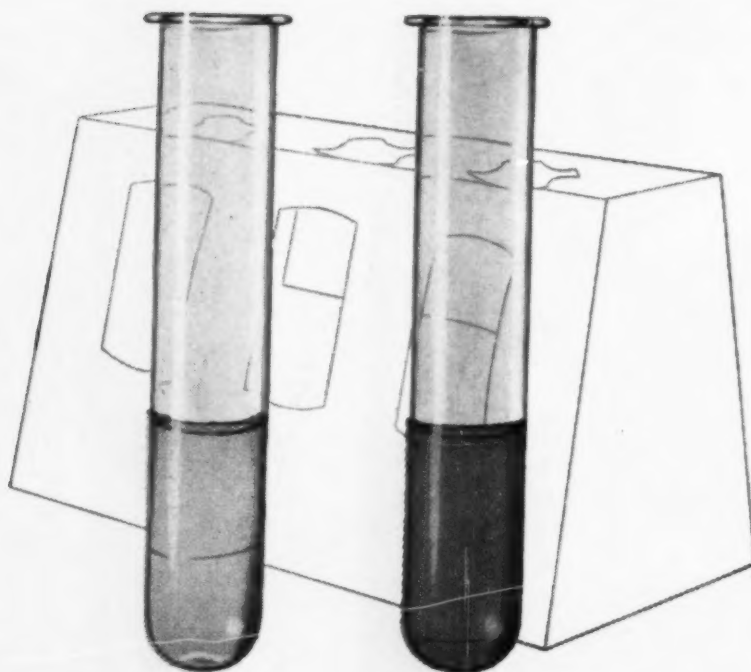


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NOW! without intubation

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as simple as **A-B-C**

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- B.** Urine samples are returned to the physician.
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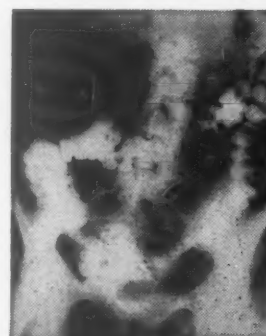
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when anxiety and tension "erupts" in the G. I. tract...

in spastic and irritable colon



PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer... helps control the "emotional overlay" of spastic and irritable colon—without fear of barbiturate loginess, hangover or habituation...with PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime. *Supplied:* Bottles of 100, 1,000.



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Arlidin is often effective when other vasodilators fail...because it brings more blood where needed most.

"The increased blood flow brought about by this drug (ARLIDIN) is predominant and lasting in skeletal muscle and quite negligible in the skin."¹

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produced improvement in rest pain and ulcers, reduction in swelling and increased walking distance in a majority of 79 patients with...

intermittent claudication

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arteriosclerosis obliterans

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(Buerger's disease)

...also effective in

abdominal aortic occlusion

chronic venous insufficiency



6 mg. tablets and 5 mg. per cc. ampuls and vials
See PDR for dosage and package sizes

1. Murphy, H. L., and Klasson, D. H.: New York
St. J. M. 57:1908, June 1, 1957

SAMPLE supply of Arlidin and reprint upon request

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division of U. S. VITAMIN CORPORATION

250 East 43rd Street, New York 17, N. Y.

protected by U.S. Patent Numbers 2,661,372 and 2,661,373

new study¹

shows why

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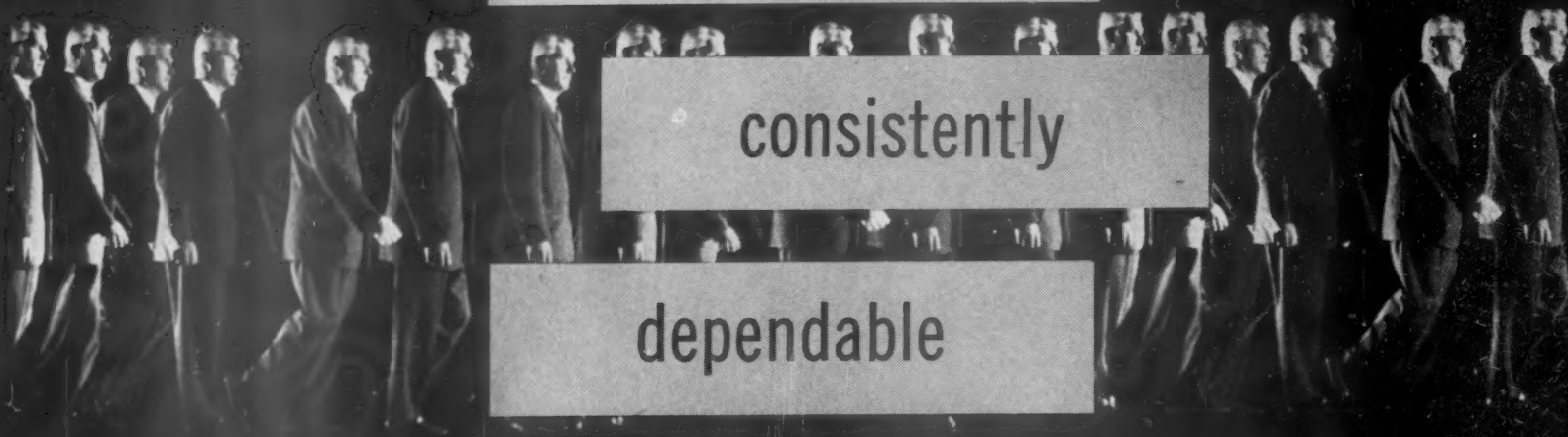
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consistently

dependable

peripheral

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Coughs due to colds or allergies are promptly relieved by BENYLIN EXPECTORANT. Combining the potent antihistaminic antispasmodic Benadryl with recognized expectorant agents, BENYLIN EXPECTORANT clears congestion, soothes irritation, and alleviates sneezing, lacrimation, and nasal stuffiness. Non-narcotic, it has a pleasant flavor acceptable to patients of all ages.

BENYLIN EXPECTORANT contains in each fluid ounce:

Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	80 mg.
Ammonium chloride	12 gr.
Sodium citrate	5 gr.
Chloroform	2 gr.
Menthol	1/10 gr.

supplied: BENYLIN EXPECTORANT is available in 16-ounce and 1-gallon bottles.

his physician prescribed

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varicose veins
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make skin
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Systemic muscle adenylic acid therapy with *My-B-Den* produces "...a continuous gradual transformation of scaling, oozing, eczematous rough skin to smooth, soft, and wrinkly skin...."* As treatment progresses, edema diminishes, pain and itching subside, and ulcers begin to heal.

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MY-B-DEN[®]
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*Lawrence, E. D.; Doktor, D., and Sall, J.:
Angiology 2:405, 1951.

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'METHEDRINE'® **in OBESITY**

means help

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begins to yield in hours

In Parkinsonism
Highly selective action...
energizing against weak-
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against sialorrhea, dia-
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Finch, J. W.: Orphenadrine (Disipal) in
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Dosage: 1 tablet (50 mg.) t.i.d.
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combination with other drugs,
smaller dosage may suffice.

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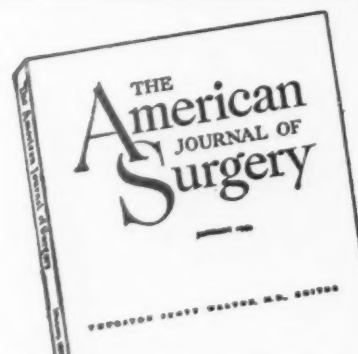
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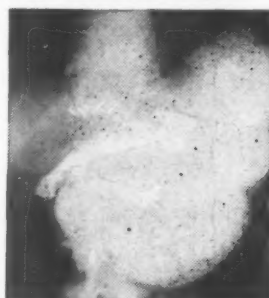
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when anxiety and tension "erupts" in the G. I. tract...

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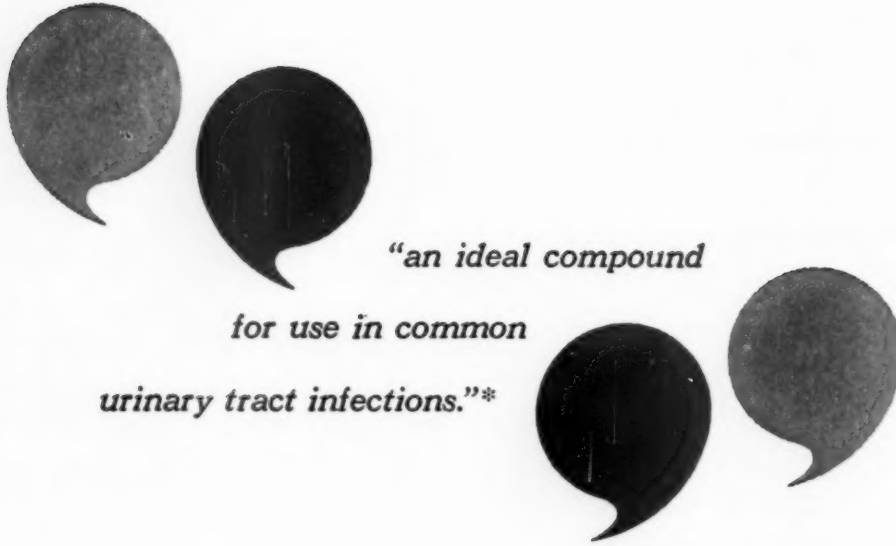
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*"an ideal compound
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Azo Gantrisin provided "prompt and effective clearing of organisms and pyuria"* plus "dramatic relief of bladder and urethral symptoms"* in 221 (97%) of 228 patients with urinary tract infections.

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*F. K. Garvey and J. M. Lancaster, North Carolina M. J., 18:78, 1957.

AZO GANTRISIN 'Roche'

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DIVISION OF HOFFMANN-LA ROCHE INC. • NUTLEY • N.J.

ORIGINAL RESEARCH IN MEDICINE AND CHEMISTRY



24 steps to a hospital bed

The commonest task, such as climbing a flight of stairs, confronts the angina pectoris patient with a fearful question: "Will I be able to make it?"

Exertion leads to attacks . . . and fear of attacks leads to an increasing restriction of activities. Ultimately, even the attack-free intervals may lose all semblance of normal living.

Remove the fear factor. In 4 out of 5 patients, routine prophylaxis with Peritrate reduces the incidence and severity of anginal attacks, improves abnormal EKG tracings and increases exercise tolerance.

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Peritrate prophylaxis is simple: 10 or 20 mg. *before meals* and at bedtime. The specific needs of most patients are met with Peritrate's five convenient dosage forms: Peritrate 10 mg. and 20 mg. tablets; Peritrate Delayed Action (10 mg.) for protection continued through the night; Peritrate with Phenobarbital (10 mg. with phenobarbital 15 mg.) where sedation is also required; Peritrate with Aminophylline (10 mg. with aminophylline 100 mg.) in cardiac and circulatory insufficiency.

Usual Dosage: A continuous schedule of 10 to 20 mg. *before meals* and at bedtime.

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(brand of pentaerythritol tetranitrate)

WARNER-CHILCOTT

new **Oral** antidiabetic agent



(Folin-Wu Test)

Used investigatively in more than 18,000 patients and demonstrated to be effective in the majority of mild, adult cases!

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natural estrogens in oral form

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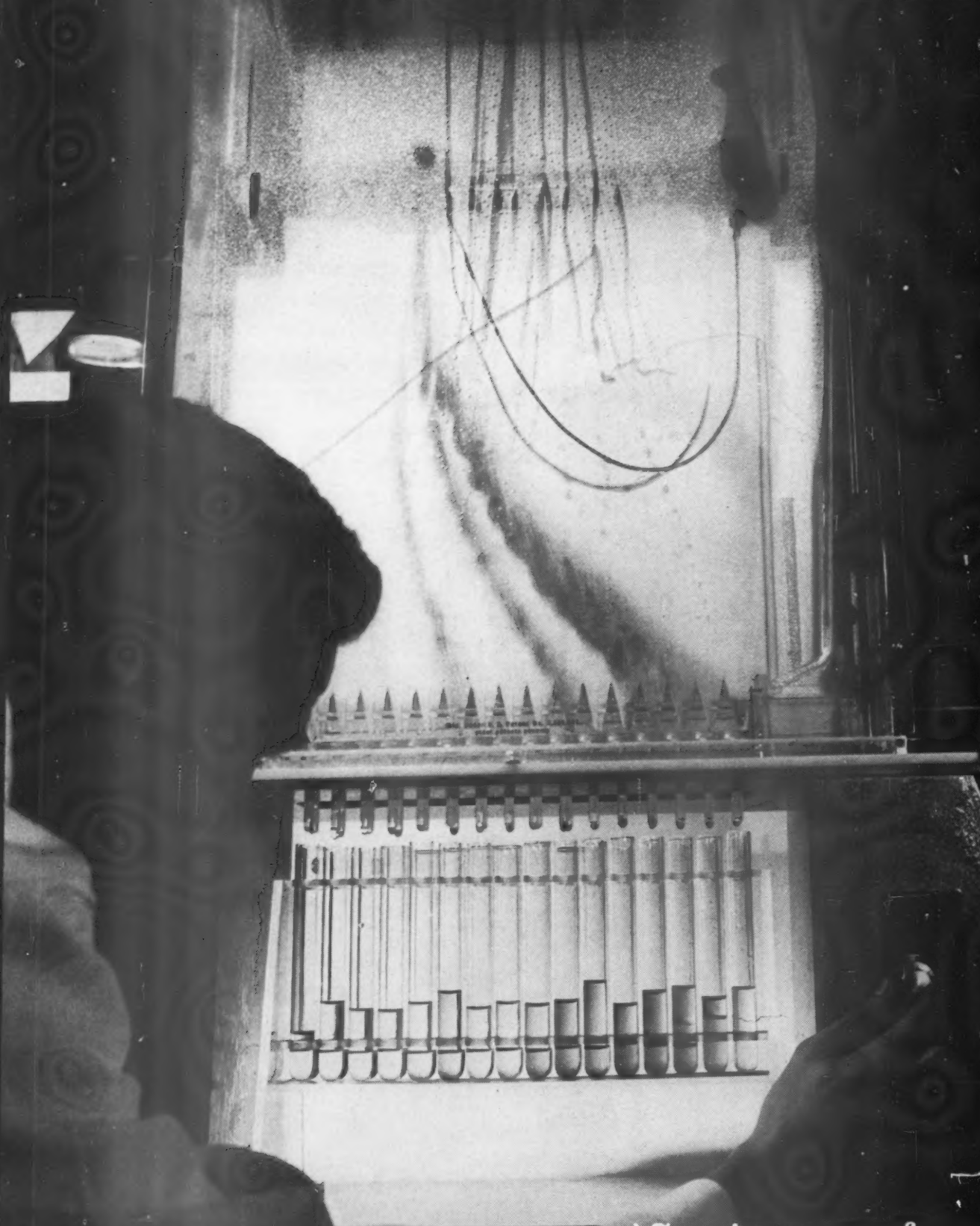
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TETREX—the original
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1. Flocks, R. H.: J.A.M.A. 163:709 (Mar. 2) 1957.

2. Flocks, R. H.; Marberger, H.; Begley, B. J.,
and Prendergast, L. J.: J. Urol. 74:549, 1955.

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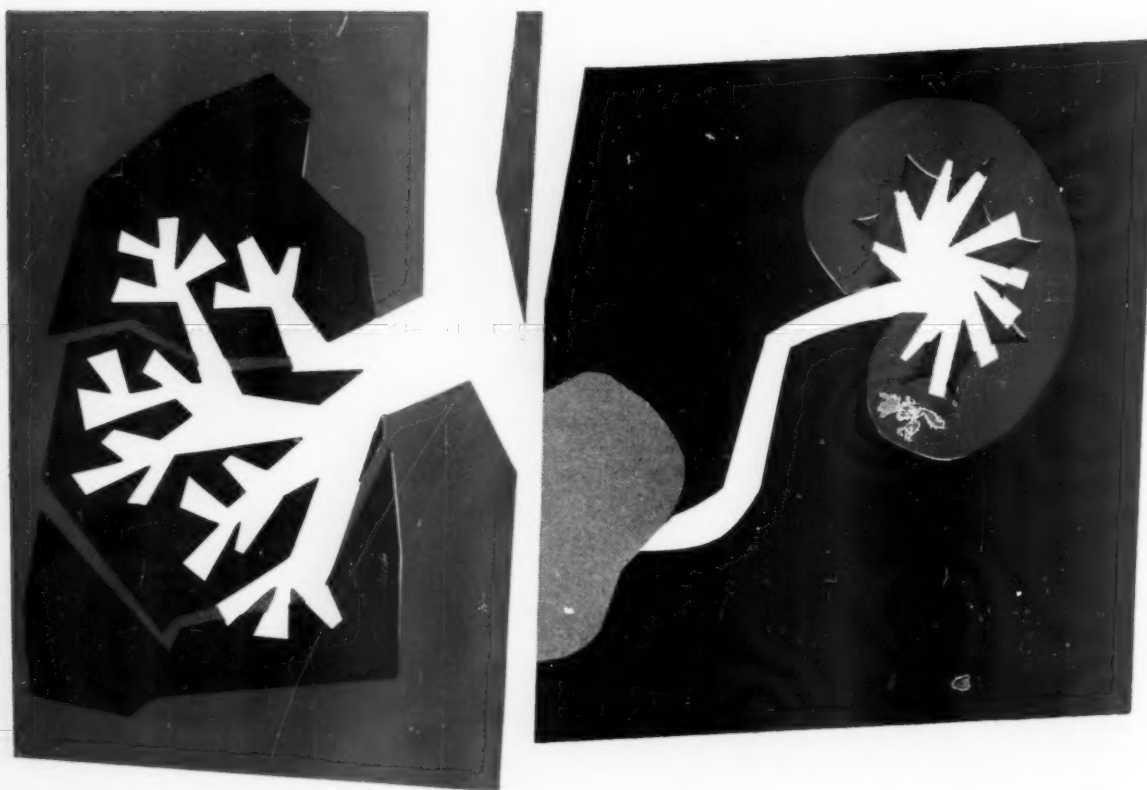
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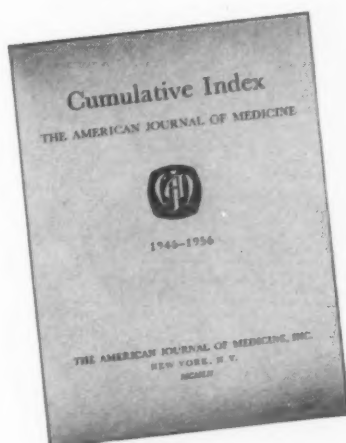
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1. Lehr, D.: Modern Med. 23:111 (Jan. 16) 1965.

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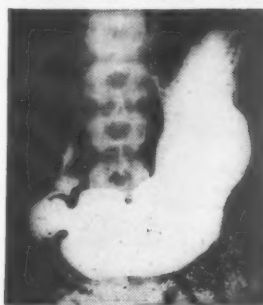
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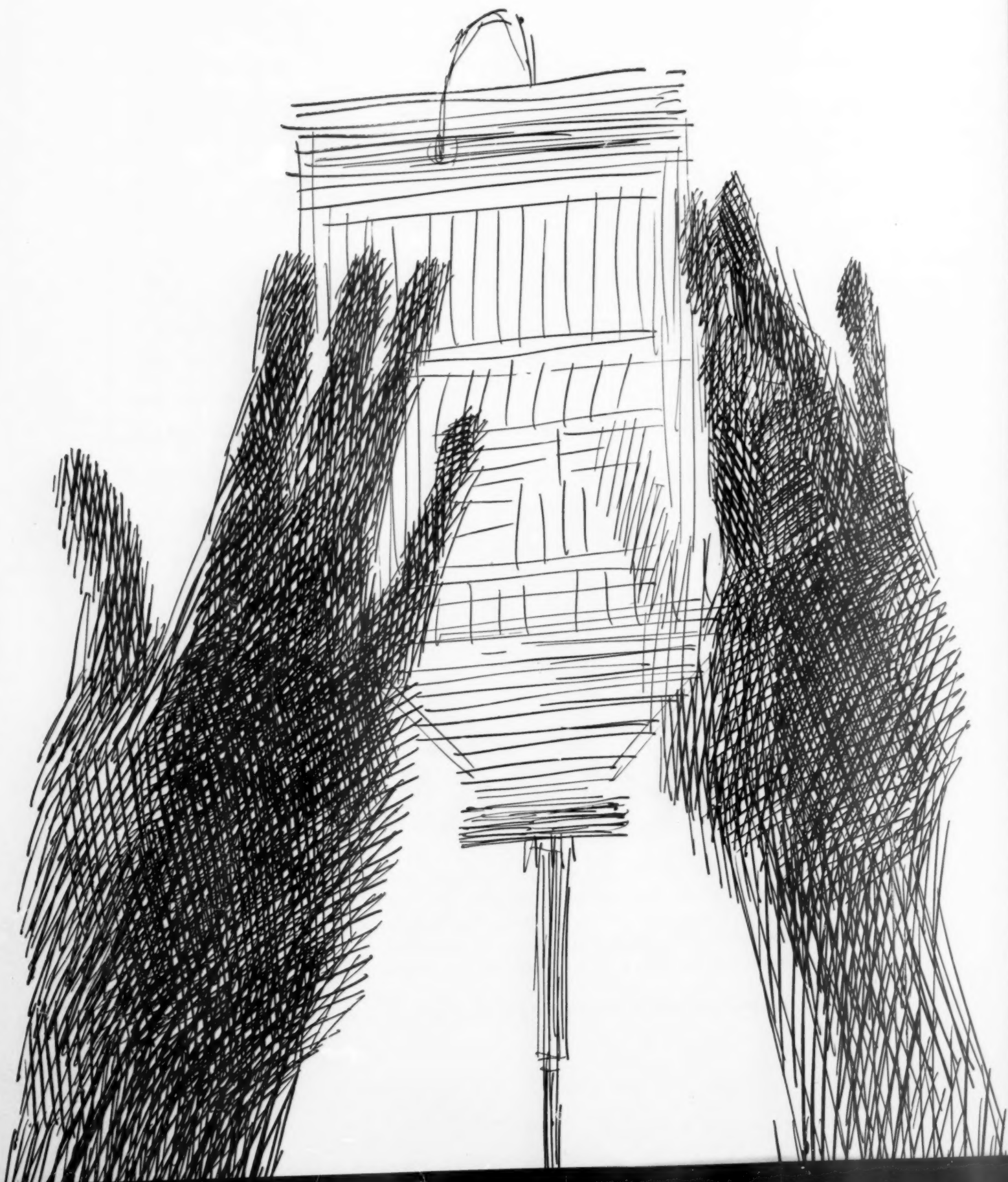
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(a) Muscle spasm secondary to sprain

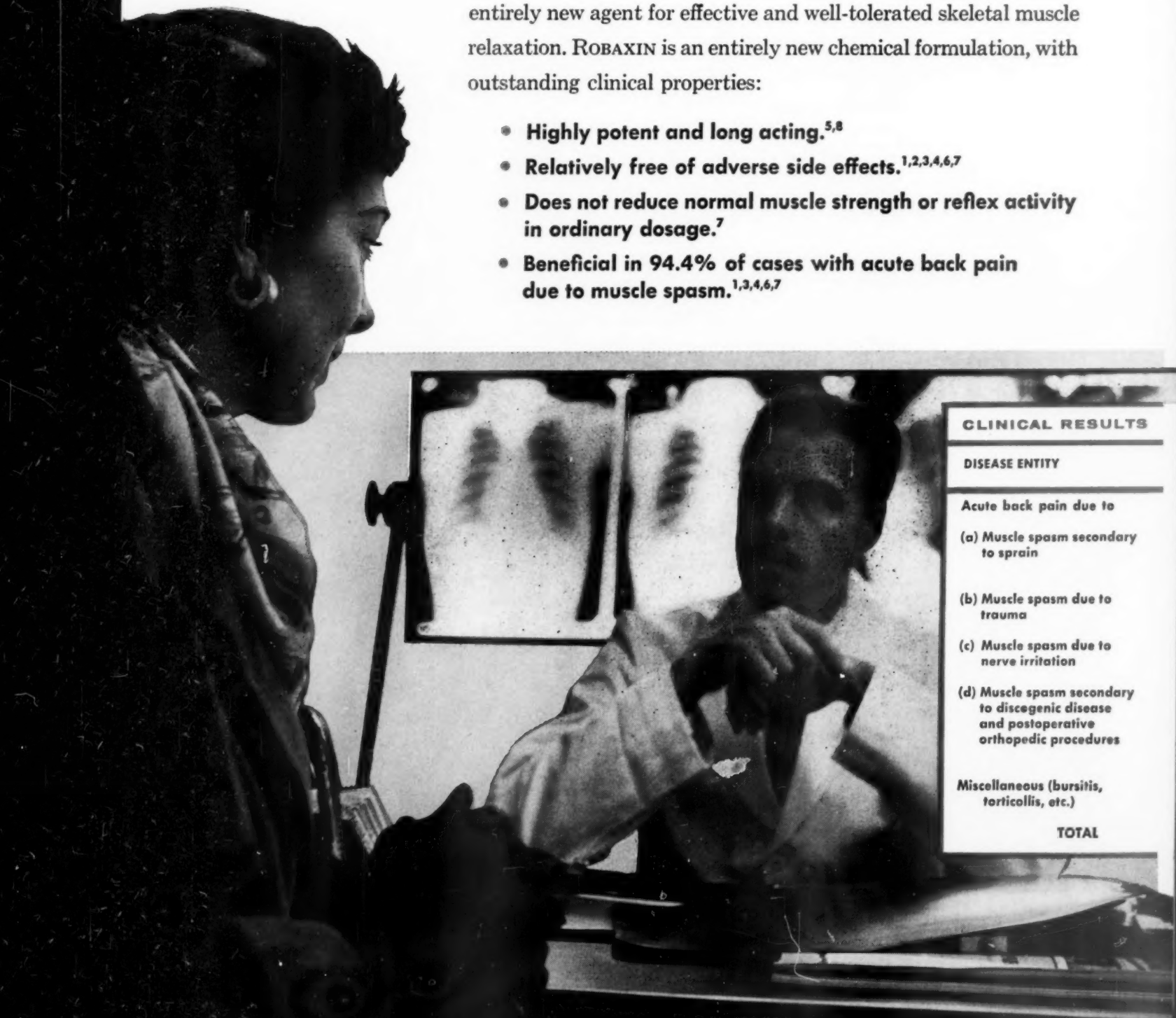
(b) Muscle spasm due to trauma

(c) Muscle spasm due to nerve irritation

(d) Muscle spasm secondary to discogenic disease and postoperative orthopedic procedures

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TOTAL





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WITH ROBAXIN IN ACUTE BACK PAIN^{1,3,4,6,7}

NO. OF CASES	DURATION OF TREATMENT	DOSE PER DAY (divided)	RESPONSE				SIDE EFFECTS
			marked	mod.	slight	neg.	
18	2-42 days	3-6 Gm.	17	1	0	0	None, 16 Dizziness, 1 Slight nausea, 1
13	1-42 days	2-6 Gm.	8	1	3	1	None, 12 Nervousness, 1
5	4-240 days	2.25-6 Gm.	4	1	0	0	None, 5
30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25 Dizziness, 1 Lightheadedness, 2 Nausea, 2 *
6	3-60 days	4-8 Gm.	6	0	0	0	None, 6
72			59	6	3	4	*Relieved on reduction of dose

References: 1. Carpenter, E. B.: Publication pending. 2. Carter, C. H.: Personal communication. 3. Forsyth, H. F.: Publication pending. 4. Freund, J.: Personal communication. 5. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: American Pharm. Assn. 46:374, 1957. 6. Nachman, H. M.: Personal communication. 7. O'Doherty, D.: Publication pending. 8. Truitt, E. B., Jr., and Little, J. M.: J. Pharm. & Exper. Therap. 119:161, 1957.

Indications — Acute back pain associated with: (a) muscle spasm secondary to sprain; (b) muscle spasm due to trauma; (c) muscle spasm due to nerve irritation; (d) muscle spasm secondary to discogenic disease and postoperative orthopedic procedures; and miscellaneous conditions, such as bursitis, fibrositis, torticollis, etc.

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1. Gibbons, T. C.: J.A.M.A. 164:22 (May 4) 1957.

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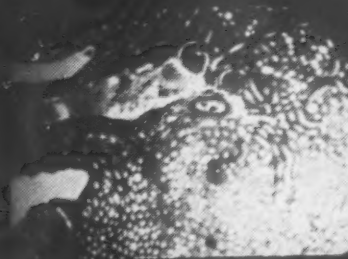
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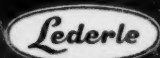
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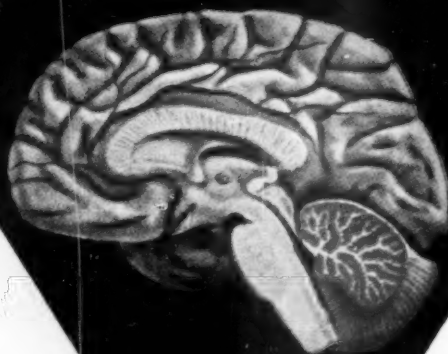


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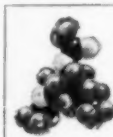
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